U.S. DEPARTMENT OF COMMERCE
National Technical Information Service

PB-261 480

PROCEEDINGS OF INTERNATIONAL SYMPOSIUM ON RECENT ADVANCES IN THE ASSESSMENT OF THE HEALTH EFFECTS OF ENVIRONMENTAL POLLUTION, HELD AT PARIS, FRANCE ON 24-28 JUNE 1974

VOLUME IV

COMMISSION OF THE EUROPEAN COMMUNITIES (LUXEMBOURG)

PREPARED FOR
ENVIRONMENTAL PROTECTION AGENCY, WASHINGTON, D.C.

1975

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA-600/9-75-009d

2.

3. RECIPIENT'S ACCESSION NO.

4. TITLE AND SUBTITLE
INTERNATIONAL SYMPOSIUM PROCEEDINGS, RECENT ADVANCES IN THE ASSESSMENT OF THE HEALTH EFFECTS OF ENVIRONMENTAL POLLUTION, VOLUME IV

5. REPORT DATE 1975

6. PERFORMING ORGANIZATION CODE

7. AUTHOR(S) U.S. Environmental Protection Agency, World Health Organization, Commission of the European Communities

8. PERFORMING ORGANIZATION REPORT NO. EUR 5360

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Comission of the European Communities
Direcotrate General Scientific and Technical Information and Information Management
Boite postal 1003, Luxembourg

10. PROGRAM ELEMENT NO. 1AA005

11. CONTRACT/GRANT NO.

12. SPONSORING AGENCY NAME AND ADDRESS
Office of Health and Ecological Effects
Office of Research and Development
U.S. Environmental Protection Agency
Washington, D.C. 20460

13. TYPE OF REPORT AND PERIOD COVERED Proceedings, June 24-28, 1974

14. SPONSORING AGENCY CODE EPA-ORD

15. SUPPLEMENTARY NOTES CONTACT: W. Talbot, 8-755-9722 (Washington, DC)
These five days of proceedings are contained in four separately bound volumes.

16. ABSTRACT

This publication (in four volumes) contains the full proceedings of this international symposium. It is printed in the original language (Dutch, English, French, German, and Italian) of the individual reports or communications presented, with an English translation of the abstract of each report. The purpose of the meeting was to evaluate the methodologies and techniques available for establishing exposure effects relationships for environmental pollutants with the goal of encouraging development of sound bases for the establishment of various approaches to protect the public health. These proceedings are made up of more than 250 scientific papers under the broad headings of: The scientific data base required to protect human health, experimental investigations, human effects studies, animal studies, metabolism interactions, indicators of exposure, population studies, toxicological studies, exposure monitoring, monitoring needs, experimental models, tissue measurements, and environmental measurements. Discussions following papers or groups of papers are also printed. An objective of the symposium was to encourage compatible methodology and data on scientific findings to help ensure that future data will be more directly applicatle to the assessment of environmental health effects.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Pollution, Air Pollution*, Toxicology* Epidemiology*, Metabolism, Interactions, Monitors*, Experimental Design*, Carcinogens, Mutagens, Noise (Sound)*, Biphenyl, Lead Poisoning*, Pesticides, Mercury Poisoning, Trace Elements, Cadmium, Asbestos, Electromagnetic Radiation.	Global Environmental Problems, International Health and Scientific Organizations.	0601 0602 0603 0606 0620 1201 1406

18. DISTRIBUTION STATEMENT RELEASE TO PUBLIC xcvi	**19. SECURITY CLASS** *(This Report)* UNCLASSIFIED	**21. NO. OF PAGES** 650
	20. SECURITY CLASS *(This page)* UNCLASSIFIED	**22. PRICE** $16.25/3.00

EPA Form 2220-1 (9-73)

Reproduced from best available copy.

351009

COMMISSION OF THE
EUROPEAN
COMMUNITIES

UNITED STATES
ENVIRONMENTAL
PROTECTION AGENCY

WORLD HEALTH
ORGANIZATION

PB 261 480

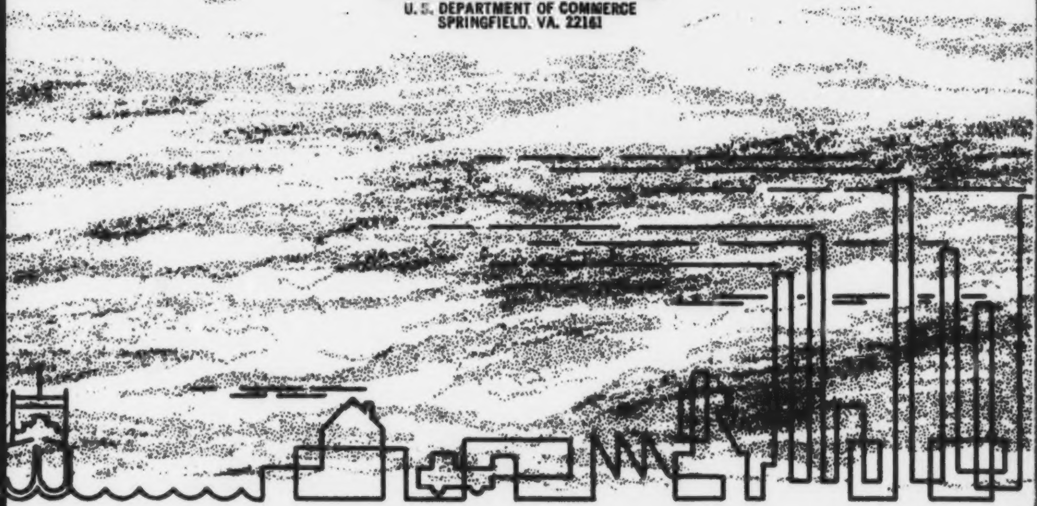
INTERNATIONAL SYMPOSIUM

PROCEEDINGS

Recent Advances in the Assessment of the Health Effects of Environmental Pollution

Volume IV

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U. S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161



Paris, 24 to 28 June 1974

EUR 5360

6.50

XCVI.a

EPA-600/9-75-009d

TAGUNGSBERICHTE
INTERNATIONALES SYMPOSIUM

NEUESTE ERKENNTNISSE IN DER BEURTEILUNG DER GESUNDHEITLICHEN FOLGEN DER UMWELTVERSCHMUTZUNG

PROCEEDINGS
INTERNATIONAL SYMPOSIUM

RECENT ADVANCES IN THE ASSESSMENT OF THE HEALTH EFFECTS OF ENVIRONMENTAL POLLUTION

ACTES
SYMPOSIUM INTERNATIONAL

PROGRES RECENTS DANS L'EVALUATION DES EFFETS DE LA POLLUTION DE L'ENVIRONNEMENT SUR LA SANTE

ATTI
SIMPOSIO INTERNAZIONALE

RECENTI PROGRESSI NELLA VALUTAZIONE DEGLI EFFETTI DELL'INQUINAMENTO DELL'AMBIENTE SULLA SALUTE

VORSLAG
INTERNATIONAAL SYMPOSIUM

RECENTE VORDERINGENBIJ DE VASTSTELLING VAN DE GEVOLGEN VAN MILIEUVERONTREINIGING VOOR DE GEZONDHEID

Paris (France), June 24-28, 1974

organized jointly by

CEC - Commission of the European Communities
Directorate General for Social Affairs - Health Protection Directorate

EPA - United States Environmental Protection Agency

and

WHO - World Health Organization

Published by the Commission of the European Communities
Directorate General Scientific and Technical Information and Information Management
Luxembourg, 1975

ORGANISATIONSAUSSCHUSS / ORGANIZING COMMITTEE / COMITÉ ORGANISATEUR COMITATO ORGANIZZATIVO / ORGANISEREND COMITÉ

Vorsitzend / Chairmen / Présidents / Presidenti / Voorzitters:

B.H. DIETERICH (W.H.O.)
S. GREENFIELD (E.P.A.)
P. RECHT (C.E.C.)

Stellvertretende Vorsizende / Vice Chairmen / Vice-présidents / Vicepresidenti / Vice-Voorzitters:

D. BARTH (E.P.A.)
M. CARPENTIER (C.E.C.)
J. KUMPF (W.H.O.)

Generalsekretär / Secretary General / Secrétaire général / Segretario generale / Algemeen Secretaris:

J. SMEETS (C.E.C.)

Wissenschaftliche Sekretariat / Scientific Secretariat / Secrétariat scientifique / Segretariato scientifico / Wetenschappelijk Secretariaat:

A. BERLIN (C.E.C.)
R. ENGEL (E.P.A.)
V.B. VOUK (W.H.O.)

Assistentin / Assistant / Assistante / Assistente / Assistent:

G. TREU-RICCO' (C.E.C.)

Wissenschaftliche Berater / Scientific advisors / Conseillers scientifiques / Consiglieri scientifici / Wetenschappelijke Adviseurs:

Ph. BOURDEAU (C.E.C.), G.C. BUTLER (Canada)
M. COLOMBINI (Italy), G. DEAN (Republic of Ireland),
J.F. FINKLEA (U.S.A.), L. FRIBERG (Sweden),
H.E. GRIFFIN (U.S.A.), W.W. HOLLAND (U.K.),
M. KEY (U.S.A.), A. LAFONTAINE (Belgium),
D. RALL (U.S.A.), H.-W. SCHLIPKÖTER (F.R. Germany),
R. SENAULT (France), J. SPAANDER (Netherlands),
L. TEPPER (U.S.A.), N.K. WEAVER (U.S.A.)

TAGUNGSBERICHTE

INTERNATIONALES SYMPOSIUM

NEUESTE ERKENNTNISSE IN DER BEURTEILUNG DER GESUNDHEITLICHEN FOLGEN DER UMWELTVERSCHMUTZUNG

Band I

ERÖFFNUNGSSITZUNG
POPULATIONSUNTERSUCHUNGEN
UNTERSUCHUNG DER WIRKUNGEN AUF DEN MENSCHEN (Panel)
TOXIKOLOGISCHE UNTERSUCHUNGEN
EXPOSITIONSMESSUNGEN (Panel)

Band II

UNTERSUCHUNG DER WIRKUNGEN AUF DEN MENSCHEN
TIERUNTERSUCHUNGEN
STOFFWECHSEL
WECHSELBEZIEHUNGEN
EXPOSITIONSINDIKATOREN

Band III

GEWEBSMESSUNGEN
ERFORDERNISSE IM HINBLICK AUF MESSUNGEN
UMWELTMESSUNGEN
EXPOSITIONSMESSUNGEN
MODELLE
ZUSÄTZLICHE BERICHTE

Band IV

DIE WISSENSCHAFTLICHEN DATENGRUNDLAGEN, DIE FÜR DIE ENTSCHEIDUNG ÜBER DEN GESUNDHEITSSCHUTZ BENOTIGT WERDEN
(Aussprache im rahmen des gesamtausschusses)
EXPERIMENTELLE FORSCHUNG
ERFORDERNISSE IM HINBLICH AUF MESSUNGEN (Panel)
GEWEBSMESSUNGEN (Panel)
UNTERSUCHUNG DER GESUNDHEITLICHEN WIRKUNGEN
SCHLUSSITZUNG
TEILNEHMERLISTE

Preceding page blank

C

PROCEEDINGS

INTERNATIONAL SYMPOSIUM

RECENT ADVANCES IN THE ASSESSMENT OF THE HEALTH EFFECTS OF ENVIRONMENTAL POLLUTION

Volume I

OPENING SESSION

POPULATION STUDIES

HUMAN EFFECTS STUDIES (Panel)

TOXICOLOGICAL STUDIES

EXPOSURE MONITORING (Panel)

Volume II

HUMAN EFFECTS STUDIES

ANIMAL STUDIES

METABOLISM

INTERACTIONS

INDICATORS OF EXPOSURE

Volume III

TISSUE MEASUREMENTS
MONITORING NEEDS

ENVIRONMENTAL MEASUREMENTS

EXPOSURE MONITORING

MODELS

SUPPLEMENTARY PAPERS

Volume IV

THE SCIENTIFIC DATA BASE REQUIRED FOR DECISIONS TO PROTECT HUMAN HEALTH (Plenary discussion group)

EXPERIMENTAL INVESTIGATIONS

MONITORING NEEDS (Panel)

TISSUE MEASUREMENTS (Panel)

HEALTH EFFECTS STUDIES

CLOSING SESSION

LIST OF PARTICIPANTS

ACTES

SYMPOSIUM INTERNATIONAL

PROGRES RECENTS DANS L'EVALUATION DES EFFETS DE LA POLLUTION DE L'ENVIRONNEMENT SUR LA SANTE

Volume I

SEANCE D'OUVERTURE
ETUDES SUR LA POPULATION
ETUDES DES EFFETS SUR L'HOMME (Panel)
ETUDES TOXICOLOGIQUES
MESURE DE L'EXPOSITION (Panel)

Volume II

ETUDES DES EFFETS SUR L'HOMME
ETUDES SUR LES ANIMAUX
METABOLISME
INTERACTIONS
INDICATEURS D'EXPOSITION

Volume III

MESURES RELATIVES AUX TISSUS BIOLOGIQUES
BESOINS EN MATIERE DE MESURE DE L'EXPOSITION
MESURES DANS L'ENVIRONNEMENT
MESURE DE L'EXPOSITION
MODELES
RAPPORTS SUPPLEMENTAIRES

Volume IV

LES DONNEES SCIENTIFIQUES REQUISES A LA PRISE DE DECISION POUR LA PROTECTION DE LA SANTE HUMAINE
(Groupe de discussion en assemblée plénière)
RECHERCHES EXPERIMENTALES
BESOINS EN MATIERE DE MESURE DE L'EXPOSITION (Panel)
MESURES RELATIVES AUX TISSUS BIOLOGIQUES (Panel)
ETUDES DES EFFETS SUR LA SANTE
SEANCE DE CLOTURE

LISTE DES PARTICIPANTS

ATTI
SIMPOSIO INTERNAZIONALE
RECENTI PROGRESSI NELLA VALUTAZIONE DEGLI EFFETTI DELL'INQUINAMENTO DELL'AMBIENTE SULLA SALUTE

Volume I

SESSIONE INAUGURALE
STUDI SULLA POPOLAZIONE
STUDI DEGLI EFFETTI SULL'UOMO (Panel)
STUDI TOSSICOLOGICI
MISURA DELL'ESPOSIZIONE (Panel)

Volume II

STUDI DEGLI EFFETTI SULL'UOMO
STUDI SUGLI ANIMALI
METABOLISMO
INTERAZIONE
INDICATORI DI ESPOSIZIONE

Volume III

MISURE NEI TESSUTI BIOLOGICI
NECESSITA' RELATIVE ALLA MISURA DELL'ESPOSIZIONE
MISURE AMBIENTALI
MISURA DELL'ESPOSIZIONE
MODELLI
RAPPORTI SUPPLEMENTARI

Volume IV

I DATI SCIENTIFICI DI BASE RICHIESTI PER PRENDERE DECISIONI AL FINE DI PROTEGGERE LA SALUTE UMANA
(Gruppo di discussione plenaria)
INDAGINE SPERIMENTALE
NECESSITA' RELATIVE ALLA MISURA DELL'ESPOSIZIONE (Panel)
MISURE NEI TESSUTI BIOLOGICI (Panel)
STUDI DEGLI EFFETTI SULLA SALUTE
SESSIONE FINALE

ELENCO DEI PARTECIPANTI

CIII

VORSLAG

INTERNATIONAAL SYMPOSIUM

RECENTE VORDERINGEN BIJ DE VASTSTELLING VAN DE GEVOLGEN VAN MILIEUVERONTREINIGING VOOR DE GEZONDHEID

Band I

OPENINGSZITTING

BEVOLKINGSSTUDIES

ONDERZOEKINGEN NAAR EFFECTEN BIJ DE MENS (Panel)

TOXICOLOGISCHE ONDERZOEKINGEN

METING VAN EXPOSIE (Panel)

Band II

ONDERZOEKINGEN NAAR EFFECTEN BIJ DE MENS

ONDERZOEKINGEN BIJ DIEREN

METABOLISME

INTERACTIES

INDICATOREN VAN EXPOSIE

Band III

METINGEN VAN BIOLOGISCH WEEFSEL

EISEN VOOR HET TOT STAND BRENGEN VAN TOEZICHT OP EXPOSIE

METINGEN IN HET MILIEU

METINGEN VAN EXPOSIE

MODELLEN

SUPPLEMENTAIRE DOCUMENTEN

Band IV

WETENSCHAPPELIJKE GEGEVENS NOODZAKELIJK VOOR HET NEMEN VAN BESLISSINGEN TER BESCHERMING VAN DE GEZONDHEID VAN DE MENS
(Plenaire discussiegroep)

EXPERIMENTEEL ONDERZOEK

EISEN VOOR HET TOT STAND BRENGEN VAN TOEZICHT OP EXPOSIE (Panel

METINGEN VAN BIOLOGISCH WEEFSEL (Panel)

ONDERZOEKINGEN NAAR GEVOLGEN VOOR DE GEZONDHEID

SLOTZITTING

DEELNEMERSLIJST

cV

INHALTSVERZEICHNIS

CONTENTS

TABLE DES MATIERES

INDICE

INHOUDSOPGAVE

Preceding page blank

DIE WISSENSCHAFTLICHEN DATENGRUNDLAGEN, DIE FUER DIE ENTSCHEIDUNG UEBER DEN GESUNDHEITSSCHUTZ BENOETIGT WERDEN (Aussprache im Rahmen des Gesamtausschusses)
THE SCIENTIFIC DATA BASE REQUIRED FOR DECISIONS TO PROTECT HUMAN HEALTH (Plenary discussion group)
LES DONNEES SCIENTIFIQUES REQUISES A LA PRISE DE DECISION POUR LA PROTECTION DE LA SANTE HUMAINE (Groupe de discussion en assemblée pléniere)
I DATI SCIENTIFICI DI BASE RICHIESTI PER PRENDRE DECISIONI AL FINE DI PROTEGGERE LA SALUTE UMANA (Gruppo di discussione plenaria)
WETENSCHAPPELIJKE GEGEVENS NOODZAKELIJK VOOR HET NEMEN VAN BESLISSINGEN TER BESCHERMING VAN DE GEZONDHEID VAN DE MENS (Plenaire discussiegroep) 1873

EXPERIMENTELLE FORSCHUNG
EXPERIMENTAL INVESTIGATIONS
RECHERCHES EXPERIMENTALES
INDAGINE SPERIMENTALE
EXPERIMENTEEL ONDERZOEK

The state of the art regarding the experimental investigations of the effects of pollutants 1967
D.V. BATES

The effects of low levels of SO_2 and ozone in the same atmosphere on human pulmonary function 1979
D.V. BATES, M. HAZUCHA

Effects of sulfur dioxide on healthy and peripheral airway impaired subjects 1989
F.W. WEIR, P.A. BROMBERG

Emergency population exposure: a methodological approach . . 2005
P.E. JOOSTING, M.M. VERBERK

L'influence du bruit sur le sommeil de travailleurs de nuit et des travailleurs par équipes alternantes 2031
P. KNAUTH, J. RUTENFRANZ

Alteration in urinary D-glucaric acid excretion as an indication of exposition to xenobiotics 2047
W.R.F. NOTTEN, P.Th. HENDERSON

The assessment of environmental carcinogen risks in terms of life shortening 2061
R.E. ALBERT, B. ALTSHULER

Preceding page blank

ERFORDERNISSE IM HINBLICK AUF MESSUNGEN (Panel)
MONITORING NEEDS (Panel)
BESOINS EN MATIERE DE MESURE DE L'EXPOSITION (Panel)
NECESSITA' RELATIVE ALLA MISURA DELL'ESPOSIZIONE (Panel)
EISEN VOOR HET TOT STAND BRENGEN VAN TOEZICHT OP EXPOSIE (Panel)

Pollutant-oriented integrated monitoring systems and lead exposure assessment 2073
E.A. SCHUCK, G.B. MORGAN, D.S. BARTH

Integrated assessment of health effects of air pollution . . 2083
L.R. BABCOCK jr, N.L. NAGDA, A.T. ROSSANO

Mexico city's pindex level 2091
H.BRAVO A, M.E. ESPINOSA, A.C. LOWE, S. SALAZAR

A method for simulating the true human exposure of critical population groups to air pollutants 2097
W.R. OTT, D.T. MAGE

Personal and indoor exposure meters 2109
A.P. ALTSHULLER, A.E. O'KEEFFE

Die automatische Ueberwachung der Kraftfahrzeugabgas-Immission im Arbeits- und Wohnbereich 2115
D. JOST, W. RUDOLF

Incorporation of population exposure concepts in air quality criteria documents 2143
A.C. STERN, Y. HORIE

Panel Discussion 2153

GEWEBSMESSUNGEN (Panel)
TISSUE MEASUREMENTS (Panel)
MESURES RELATIVES AUX TISSUS BIOLOGIQUES (Panel)
MISURE NEI TESSUTI BIOLOGICI (Panel)
METING VAN BIOLOGISCH WEEFSEL (Panel)

Intercomparison programme on the analysis of lead, cadmium and mercury in biological fluids 2185
A. BERLIN, R. LAUWERYS, J.P. BUCHET, H. ROELS,
P. Del CASTILHO, J. SMEETS

A comparison of methods for analysis of cadmium in food and biological material. A co-operative study between Sweden, Japan and U.S.A. 2197
T. KJELLSTRÖM, K. TSUCHIYA, E. TOMPKINS, F. TAKABATAKE
B. LIND, L. LINNMAN

The determination of lead and cadmium in blood by atomic absorption spectroscopy 2215
H.T. DELVES

Mesure du plomb dans les os humains provenant de la région parisienne 2225
L. JEANMAIRE, F. PATTI, N. CIALELLA, R. GROS

Zur Blei- und Cadmiumanalytik in biologischen Matrices . . . 2231
M. STOEPPLER, F. BACKHAUS, R. DAHL, M. DUMONT,
H. HAGEDORN-GOETZ, K. HILPERT, P. KLAHRE, H. RÜTZEL,
P. VALENTA, H.W. NUERNBERG

Panel Discussion 2247

GEWEBSMESSUNGEN (Panel)
TISSUE MEASUREMENTS (Panel)
MESURES RELATIVES AUX TISSUS BIOLOGIQUES (Panel)
MISURE NEI TESSUTI BIOLOGICI (Panel)
METING VAN BIOLOGISCH WEEFSEL (Panel)

The concentrations of copper, iron, manganese, zinc and cadmium in human hair as a possible indicator of their tissue concentrations 2263
E. VUORI, A. HUUNAN-SEPPALA, J. KILPIÖ

Trace elements in lung and hair 2271
G.W. GIBBS, E. BOGDANOVIC

Trace metal content of hair and the levels of 5-HIAA in the urine of population exposed to lead 2285
B. STANKOVIC, M. STANKOVIC, S. MILIC, Z. KORICANAC,
Lj. MILOVANOVIC, M. DUGANDZIC

Panel Discussion 2293

UNTERSUCHUNG DER GESUNDHEITLICHEN WIRKUNGEN
HEALTH EFFECTS STUDIES
ETUDES DES EFFETS SUR LA SANTE
STUDI DEGLI EFFETTI SULLA SALUTE
ONDERZOEKINGEN NAAR GEVOLGEN VOOR DE GEZONDHEID

Health effects studies - now and in the future 2307
L. FRIBERG

The carcinogenic risk for man of environmental chemicals . . 2317
L. TOMATIS

Interaction of environmental chemical, enzymatic changes and their possible effects on health 2331
H.L. FALK

Perspectives in the environmental toxicology of trace metals 2351
K. TSUCHIYA

Assessment of the influences of environmental pollutants on cancer and other chronic diseases 2367
S.S. EPSTEIN

The use of quantitative EEG for detecting low-level prolonged exposure to pesticides 2387
J.A. SANTOLUCITO

Internal pollution - Our first priority. A review of the studies of the special commission of internal pollution 2397
P. BEACONSFIELD, N. BORLAUG, A. CAPRI DI RISMINI, H. KREBS, R. PETERS, R. RAINSBURY

A comprepensive toxicological limitation of toxic substances in the environment. Functional and metabolic criteria of noxious action. 2409
N. IZMEROV, I.V. SANOTSKY

Behavioral methods for investigating environmental health effects 2415
B. WEISS

SCHLUSSITZUNG
CLOSING SESSION
SEANCE DE CLOTURE
SESSIONE FINALE
SLOTZITTING

Conclusions et réflections des conseillers scientifiques. . . . 2437
A. LAFONTAINE

B.H. DIETERICH 2451
Director Division of Environmental Health, World Health Organization

A.C. TRAKOWSKI 2455
Assistant Administrator for Research and Development - United States Environmental Protection Agency

P. RECHT 2461
Directeur de la Protection Sanitaire - Commission des Communautés Européennes

TEILNEHMERLISTE - LIST OF PARTICIPANTS - LISTE DES PARTICIPANTS - LISTA DEI PARTECIPANTI - LIJST VAN DE DEELNEMERS 2469

Aussprache im Rahmen des Gesamtausschusses - Plenary Discussion Group - Groupe de Discussion en Assemblée pléniere - Gruppo di Discussione Plenaria - Plenaire Discussiegroep

DIE WISSENSCHAFTLICHEN DATENGRUNDLAGEN, DIE FUER DIE ENTSCHEIDUNG UEBER DEN GESUNDHEITSSCHUTZ BENOETIGT WERDEN

THE SCIENTIFIC DATA BASE REQUIRED FOR DECISIONS TO PROTECT HUMAN HEALTH

LES DONNEES SCIENTIFIQUES REQUISES A LA PRISE DE DECISION POUR LA PROTECTION DE LA SANTE HUMAINE

I DATI SCIENTIFICI DI BASE RICHIESTI PER PRENDERE DECISIONI AL FINE DI PROTEGGERE LA SALUTE UMANA

WETENSCHAPPELIJKE GEGEVENS NOODZAKELIJK VOOR HET NEMEN VAN BESLISSINGEN TER BESCHERMING VAN DE GEZONDHEID VAN DE MENS

Chairman :

D.S. BARTH	U.S. Environmental Protection Agency, National Environmental Research Centre, Las Vegas, Nevada, U.S.A.

Members :

D. BENINSON	Gerencia de Proteccion, Radiologica y Seguridad, Buenos Aires, Argentina
K. BIERSTEKER	Municipal Health Department, Rotterdam, Nederland
G.C. BUTLER	Division of Biological Sciences, National Research Council of Canada, Ottawa, Ontario, Canada
J.R. GOLDSMITH	National Cancer Institute and California State Health Dept., Bethesda, Maryland, U.S.A.
P. RECHT	Commission des Communautés Européennes, Direction Protection Sanitaire, Luxembourg
J. TREMOLIERES	Laboratoire de Nutrition Humaine, Institut National de la Santé et de la Recherche Médicale, Hôpital Bichat, Paris, France
V.B. VOUK	World Health Organization, Division of Environmental Health, Geneva, Helvetia

THE SCIENTIFIC DATA BASE REQUIRED FOR DECISIONS TO PROTECT HUMAN HEALTH

(Chairman's Note)

D. S. BARTH

The purpose of the Plenary Discussion Group was to provide a forum for discussion of the interface between scientists doing research to assess health effects of environmental pollutants and decision makers who must use the resulting information to develop adequate environmental protection plans. Each member of the Plenary Discussion Group was selected on the basis of his scientific expertise and was asked to represent his personal views and convictions in responding to questions and in discussing issues. Thus, the answers provided to questions represented the personal views of the individual responders and not the collective views of the entire Plenary Discussion Group.

Each member of the Group was given an opportunity for an opening statement to address those issues which he considered to be of the highest priority. They were requested to consider the following topics as part of their opening statement:

- What is the contribution and significance of epidemiological, clinical and toxicological studies in determining protection guides?
- In determining exposure-effect relationships, what is the relative importance of parameters such as age, race, state of health, nutritional status and eating habits, climate, occupation, smoking history, socioeconomic status, etc?
- How important are biological responses, such as increases in pollutant burden or physiological effects of uncertain significance, in setting protection guides?
- In the development of protection guides, how does one account for the difference between acutely toxic

Preceding page blank

and cumulatively toxic environmental pollutants?

- How should exposure-effect relationships be expressed and analyzed to be most helpful in developing protection guides? Is a "threshold" or a "non-threshold" concept preferable?
- Is it possible to account for, or correct for, concurrent exposure to multiple pollutants which may be synergistic or antagonistic?
- What factors go into determining an adequate margin of safety for a protection guide?
- What factors go into determining meaningful relationships between public health protection guides and occupational health protection guides?
- should a fixed value be set as a protection guide or should a range of values be given?
- What are the population groups (aged, children, diseased, etc.) to be considered in proposing protection guides for different pollutants?
- What is the importance of indoor measurements vs. outdoor measurements in determining exposure?
- Is it possible to relate one study to another when different measurement methods were used to assess either exposure or effects?

Following these presentations, questions which had been previously submitted in writing by the participants were answered by one or more members of the Group. The original questions asked in writing by the participants at this Symposium are reproduced at the end of this session. The Panel Members and the Scientific Secretariat met prior to the plenary session to summarize and combine the original questions into a fewer number so all subject areas germane to this discussion could be covered within the time allotted. During the course of answering the panel questions, it became apparent that there would not be sufficient time to allow oral questions and discussions from the floor. The Chairman, feeling that oral participation by Symposium participants was desirable, deferred answering some of the panel questions with the promise that all questions not answered during the session would be answered in the Proceedings. Thus, the last part of the session was devoted to oral interchanges between participants and members of the Group. At the conclusion of the session, there were many participants still asking for recognition to bring up additional questions. To accommodate these additional questions, the Group agreed to accept pertinent written questions after the session with the promise that all such questions would be answered in the Proceedings.

OPENING OF THE PLENARY GROUP DISCUSSION

BARTH

As Chairman, I would like to call this session to order please. This is the Plenary Discussion Group on the subject 'the Scientific Data Base Required for the Decisions to Protect Human Health'. First I would like to read from a document which was prepared by the Scientific Advisors, to advise the organizing committee with regard to the purpose of such a session as this. Specifically the words are as follows: 'as stated in the announcement the symposium is of particular interest for all those concerned with the public health and research aspects of environmental pollution as well as those concerned with its control. The purpose of this panel session is to develop strategies for organising the scientific knowledge of the exposure-effect relations for the development of criteria.' This discussion should therefore address itself to three aspects of the scientific data required by administrators. First is the kind of data required. Ideally the administrator should be provided with estimates of the probability of the effects produced in a variety of receptors by each pollutant. How the data are presented will determine his course of action. Second is the quantitative description of the damage. The description should be given as an estimate of absolute risk.

This can then be converted to a relative risk and compared with other risks to the same population. Finally, crucial lacks in the data base must be identified, ordered in priority and considered in planned research.

In a letter that I sent to the members of the Plenary Discussion Group, I wrote the following paragraph, which is just an extension of what we have stated. "The purpose of this Plenary Discussion Group will be to provide an interchange between the assessment of details, scientific data and the decisions required for the protection of human health from environmental pollutants." Today our discussion must come to grips with the kinds of questions facing decision makers and how best to furnish technical information in terms which will be understandable to them. Philosophical concepts are necessary, but wherever possible the discussion should refer to practical guidelines for real situations.

Each member of the group will have an opportunity to make some introductory remarks and each member is asked to limit those remarks to less than five minutes. Following the statement from each one of the members, we will then proceed to answer written questions which have been submitted to us from the floor. Because of the number of questions and the large area of subject matter, I will read a condensed paraphrased version of the submissions. I think that those of you who wrote the questions will recognize your subject.

BENINSON

The basic objectives of protection are to prevent the occurrence of deterministic effects (acute or late) and to limit the probability of occurrence of stochastic effects to levels deemed to be acceptable. The first of these objectives is easily met due to the existence of thresholds and probably exposure rate effects. The second objective relates to much more complicated problems, mainly due to the absence of human data, particularly at the levels of risk which would be considered safe. As it has been the normal practice in radiation protection, it is possible here to adopt a conservative assumption, namely, that a non-threshold linear relationship exists between the exposure and the probability of such late effects as the induction of malignancies and deleterious hereditary effects. Furthermore it can be assumed that the risk per unit exposure which might be deduced from observations at high exposures apply to the low exposure range relevant for protection.

An implicit consequence of these assumptions is that no exposure is absolutely safe. The main issue is therefore the acceptability of the implied risks, in relation to both the acceptability of other risks by society and the benefits expected from the operations causing the exposure.

At the low risk levels relevant for protection, the following basic information appears to be required for setting limits:

- adequate exposure parameters (probably time integrals of concentration of the pollutant in the critical organs)
- risk-exposure relationships (at least for high exposures, which could be conservatively assumed to apply at low exposures)
- a selection of an "acceptable" level of risk for members of the public.

As many possible effects can be due to a given pollutant, a parameter quantifying the total impact may be required.

Using the approach developed for radiation protection, the total impact could be represented by the "detriment" as originally defined by the ICRP. The "detriment" in a population is the expectation of harm incurred from an exposure taking into account not only the probabilities of each type of deleterious effect but the severity of the effects as well. Thus if P_i is the probability of suffering the effect i, the severity of which is expressed by a weighting factor g_i, then the detriment G in a group composed of P persons is = $P\Sigma(p_i\ g_i)$. Under the assumption of linearity of each p_i with exposure $p_i = r_i E$(where r_i is a risk coefficient), and further assuming that the severity of stochastic effects is independent of their frequency, the detriment can be expressed as $G = PE\Sigma(r_i g_i)$, where the sum is a constant for each pollutant.

In addition to limits of exposure (Primary Protection Standards) it is necessary to derive limits for discharge of pollutants and for levels in the environment. The use of environmental models allows the establishment of relationship between discharges, environmental levels and exposures. The basic data required are the transfer parameters relating compartments of the model.

As in the case of radiation protection, when more quantitative toxicological and ecological data become available, further requirements of protection will have to be taken into account, namely the "justification" of a given practice and the "optimization" of protection.

Assessing the justification of a given source involves cost-benefit analysis considering its total positive and negative effects as well as the availability of alternative procedures. The optimization of protection, on the other hand, is assessed by differential cost-benefit analysis, with the purpose of finding the lowest reasonably achievable exposure. This is obtained when the costs of further reduction outweigh the achieved reduction of detriment. Both types of cost-benefit analysis require the assignment of a monetary cost per unit exposure. This is a very complex problem, but some values have been published at least in the field of radiation protection and similar values could be derived for other pollutants if the exposure-risk relationships become available.

BIERSTEKER
Environmental health can be defined as the collection of scientifically sound data that can help man in establishing positive relations with his environment, leading to better health and welfare, now and in future generations.

The first part of this definition is a means, the second a goal or objective. About the objective exists little difference in public health circles, though health is harder to define than in the past, when indicators like the infant mortality rate, life expectancy and incidence of communicable diseases were simple yardsticks. Nowadays the content of life seems to gain in importance and it is not unusual that large numbers of people are willing to trade in a few months or even one or two years of life expectancy for a beautification of the remaining years.

To study the means of our definition, we have to collect data that demonstrate qualitative and quantitative relations between man and his environment. So far this has been mainly the task of epidemiologists. Thanks to the work of a relatively small number of scientists, the role of the environment in the transmission of communicable diseases has been successfully documented and communicable disease control possesses enough scientifically sound data to control diseases like poliomyelitis, measles, diphtheria, rubella, smallpox, whooping cough, malaria, schistosomiasis, cholera, typhoid fever, etc.

When we look at these victories, insiders realize, however, that in the list of diseases which I mentioned, the environment often plays a minor role, at least from the standpoint of control. In many cases the environment is left untouched, for instance when vaccination is used as the main tool to prevent communicable diseases. In other control programs the focus is on only a very small part of the environment. Malaria control, for example, does not aim at Anopheles eradication but at elimination of those members of the malaria parasites transmitting species, which have just taken a blood meal from a potential parasite carrier.

The fact that malaria eradication and schistosomiasis eradication are so much harder to achieve than smallpox and diphtheria eradication, is due to the fact that the the environment plays a more important role in the transmission of the first two diseases. The difference is also due to the fact that man himself plays an active role in malaria and schistosomiasis eradication. If he does not participate fully due to lack of understanding or simply unwillingness, the eradication becomes a doubtful goal. Where this cooperation means a change in his way of life, in his habits, the risk of failure increases enormously.

The relation between man and his chemical environment is much less understood than the relationship between man and his environmental microbes. This should caution us against a too optimistic view of the contribution that medicine can make in this non-communicable sector of environmental health. Even where we succeed in establishing true cause and effect relations, control may be difficult because control means a change in his way of life, in his philosophy, and in the values he places on things. To achieve an environment safe for health, there will be no easy victories as were obtained by vaccination, chlorination of water supplies, indoor spraying of DDT, etc. It will take scientific data about man at risk from the environment as well as about the environment at risk from man. And it will take data about means to make man change his way of life.

The contribution this meeting makes is mainly in the first of these three fields of action; i.e., data acquisition about the effect of chemical pollutants in the environment on mans' health. A large number of epidemiological studies has been necessary to elucidate such simple questions as: where do populations begin to show an increase in respiratory disease prevalence or incidence if we measure sulfur oxides and smoke as indicators of pollution. From the standpoint of public health, smoke and sulfur oxides can never do good to a human lung. The fact that we study the relationships is already a concession. Society expects data on which it can base an ethical judgment. We do not know at what prevalence or incidence society wants action, but we all know that there is a sentimental feeling about the physically weak in a society. The standards for air pollution that society wants seem in the first place to aim at the protection of people with existing cardio-respiratory impairments. For the long term exposure standards we even lack proof whether effects are due to the short increases in pollution or to the chronic load of small particles that exists in such environments. Surprisingly enough, the same lack of insight exists about oxidants. Whether the intermittent exposure has long term effects is still a matter of doubt. We are somewhat better off with specific pollutants like carbon monoxide and lead, where biological responses can be reproduced in the laboratory, though the public health significance of the responses that have been used for standard setting may in the long run not impress society sufficiently to act on these data alone.

The problem illustrated by these few examples is that we are lacking data in three fields:

- what standards does society exactly want to set to protect environmental health,
- what effects does man even after setting such standard s possibly still have on the environment,
- what means do we have to make man cooperate in keeping the standards.

The possibility exists that man's effect on the environment takes place at levels of exposure which are not directly detrimental to his health as expressed in terms of life expectancy or prevalence of known diseases. The beautification of life, or the contrast of it and the absence of beauty due to malodors or hazes or needless noise for example, so far has not been expressed in standards, though we know that more people in polluted environments are aware of a problem. It is, based on my Rotterdam experience, possible that the movement for better environmental health finds its real roots in a welfare society. This would mean that standards for direct physical health risks are needed. But also data to set standards for beautification of the environment. Every general practitioner nowadays deals more and more with patients who are not ill in the classical way but who are considered ill from deficiencies in their social and physical environment. In this meeting we have talked about the physical environment mainly, and it will probably be an easier field to remedy than the social field.

For the ever changing human behavior, we may well need more help from the social disciplines than we realize at this moment. I fear, however, that their data collection for the successful implementation of environmental health projects has hardly begun.

BUTLER

The purpose of this Plenary Discussion Group should be to initiate a dialogue between scientists and administrators involved in environmental affairs. To begin with they should use the same vocabulary and I propose to use that recommended for the Stockholm Conference. Since there is at present no standard usage, a number of terms have been defined by the Preparatory Committee for the discussion of international co-operation for pollution control at Stockholm:

- exposure: the amount of a particular physical or chemical agent that reaches the target;

- *target* (or *receptor*): the organism, population or resource to be protected from specified risks;
- *risk*: the expected frequency of undesirable effects arising from a given exposure to a pollutant;
- *criteria* (or *exposure-effect relationships*): the quantitative relations between the exposure to a pollutant and the risk or magnitude of an undesirable effect under specified circumstances defined by environmental variables and target variables;
- *primary protection standard*: an accepted maximum level of a pollutant (or its indicator) in the target, or some part thereof, or an accepted maximum intake of a pollutant or nuisance into the target under specified circumstances;
- *derived working levels* (or *limits*): maximum acceptable levels of pollutants in specified media other than the target designed to ensure that under specified circumstances a primary protection standard is not exceeded;
    - derived working levels are known by a variety of names, including *environmental* or *ambient quality standards, maximum permissible limits* and *maximum allowable concentrations*. When derived working levels apply to products such as food or detergents, they may be known as *product standards*;
- the maximum acceptable release of a pollutant from a given source to a specified medium under specified circumstances may be termed a *discharge* (or *effluent* or *emission) standard* or a *release limit*. *Effluent charges* levied on the release of pollutants and *materials* taxes or prices adjustments levied on materials which may become pollutants may also be used to limit the release of pollutants;
    - in order to meet discharge standards or release limits, it may be necessary to set various types

of technological standards or codes of practice concerned with the performance and design of those technologies or operations leading to the release of pollutants; or

- derived working levels and the various means used to meet them are collectively termed derived standards and other controls;
- action level: the level of a pollutant at which specified emergency countermeasures, such as the seizure and destruction of contaminated materials, evacuation of the local population or closing down the sources of pollution, are to be taken.

It is perhaps also necessary to define "critical organ" as "the organ in which the entry of a given pollutant into the body results in the greatest body injury. This is often, but not always, assumed to be the body organ in which there is the greatest concentration of pollutant." This will depend on the nature and chemical form of the pollutant and its route of entry into the body. It is also necessary to define "threshold", which means that below some finite level of dose there is no observable effect. Certain other terms that I use will reflect my background in radiation protection and will be different from those used by many toxicologists and environmental protection officers.

In organizing his knowledge of the consequences, for human health, of environmental contamination the scientist thinks first of exposures and effects in the critical organ, where this can be identified, and how these vary with time. Where the critical organ cannot be identified the scientist may be reduced to observing symptoms displayed by the whole animal. Thus exposures may be brief or protracted (sometimes chronic) depending on: the residence of the subject in the polluted environment, the persistence of the contaminant in the environment and the chemical form and route of entry of the pollutant.

Effects can be classified into three types depending on the time course of pollutant level and its effects in the critical organ:

- Early (sometimes called "acute") effects result from a transient peak of pollutant concentration in the critical organ followed immediately by a peak of effect which, if it is not fatal, subsides rapidly. The plots of concentration vs time and effect vs time can be made if one knows the retention equation for the agent in the critical organ and the persistence of the effect as a function of time. Short-lived effects of short-lived agents usually result from the reduction of the rate of some vital process. The dose-effect curves usually display a marked threshold. Examples of such agents are: cyanide, parathion and caffeine. The kind of protection guide required for this effect should ensure that the instantaneous concentration in the critical organ never rises above the threshold which could be provided by a limit on concentration in the environment.
- Late effects may result from the build-up of the pollutant concentration in the critical organ to a maintained level which produces a commensurate damage in a proportion of the cells. Under constant intake the tissue concentration increases with time until it becomes constant at some equilibrium level. When the level of pollutant concentration and proportionate damage are high enough the symptoms appear. From a knowledge of the retention equation for the agent in the critical organ and the rate of uptake one can calculate the tissue concentration for any given time or what level of uptake will lead to what equilibrium level. Examples of agents that behave in this fashion are methyl mercury and warfarin. Environmental protection guides for such agents should limit the product of concentration and time of uptake so as to prevent the equilibrium level in the critical organ exceeding

the threshold for damage. For constant uptake there should be a limit on environmental concentration while for intermittent uptakes there should be a limit on the total concentration X time for all the episodes.

- "Stochastic" effects is the name sometimes given to effects that accumulate with little repair throughout the life of the receptor and are produced in proportion to the amount of the agent in the critical organ, however small. Here the dose-effect curve shows no threshold and the effect will be proportional to the prior time integral of agent concentration in the critical organ, whether it resulted from a single, multiple or chronic exposure. This independent variable can be calculated from the retention equation for the agent in the critical organ. The environmental protection guide for this type of effect should ensure that the subject does not receive during his lifetime an accumulated exposure that will result in an unacceptable risk of stochastic effect, usually cancer, mutation or foetal damage. Examples of such agents are: ionizing radiations or radioactive nuclides and carcinogenic hydrocarbons which produce cancer. Another type is organic phosphorus compounds such as triorthocresyl phosphate which produce permanent paralysis.

There are other examples of different combinations of persistence of agent and its effects; e.g., alcohol with a short persistence but the effects of which accumulate and DDT with a long persistence and short-lived effects.

It is apparent that of primary interest to the scientist is the time pattern of concentration of the agent (pollutant) in the critical organ and the primary protection standards to limit this to acceptable levels commensurate with acceptable risks of damage. The administrator has a greater need for derived working limits which for industrial workers could be the amount of agent excreted per day and for the population, ambient quality standards to limit intake.

Ideally, criteria reports from the scientist to the administrator should give the probability of effects for a range of levels of pollutant, with confidence limits. The administrator also needs to know how these vary with:

- the state of the subject; e.g., age, health and nutrition,
- the presence of other co-acting pollutants,
- other environmental factors such as temperature, sunlight, humidity.

This type of information, among others, is required for deciding what safety factors to use in extrapolating from the experimental results to acceptable levels for protection guides.

So far I have mentioned only the scientific information required for primary protection standards, derived working limits and ambient quality standards. In controlling pollution it may be easier to impose emission standards instead of the above protection guides, for which the administrator must have in addition quantitative information on the relation between the rates of emission and the probabilities of their occurrence on the one hand and the uptake by the receptor on the other.

The kind of information described above for pollutants and their effects as functions of time is also needed for current and candidate pesticides in order to make intelligent decisions about replacing "dangerous" or too persistent agents such as DDT with "less dangerous" or less persistent pesticides.

GOLDSMITH

The main purpose of assessment of carcinogenic effects of pollutants is to provide a basis for intervention. This requires evaluation of epidemiological and experimental evidence in response to a variety of findings. The major types of findings may be excess cancer occurrence among a population, (epidemiological evidence) or the finding of a known carcinogen to which exposure by one or more routes is occurring. While the paper does not evaluate the carcinogenic effects of occupational exposures, occupational exposures both interact with non-occupational exposures, as well as provide many of the findings of the first type.

The procedures used in evaluation of possible relationships of air pollutants and respiratory cancer and in asbestos ingestion and gastro-intestinal cancer are used to illustrate the principles of evaluation. The procedures require the application of judgment, and hence different conclusions from such procedures can be expected from different individuals and groups.

Environmental exposures, including occupational ones, have been epidemiologically associated with cancer of sinuses, pleura and peritoneum, mouth, skin, bladder, lung, larynx, liver, scrotum and with leukemia, (1). The IARC is publishing a series of monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man (2). The experts who evaluate the human effects data usually do not find such data adequate. In most examples to date, the evaluation of human health effects refers to occupational exposures.

Several decades of human exposure to environmental agents are usually required before cancer manifests itself, and this property of human cancer is one of the reasons why it is hazardous to draw quantitative or even qualitative inferences for man from experimental research. Reliance on epidemiological evaluation is therefore an important basis for conclusions. However, the epidemiologically detectable increases in cancer are often not recognized and responded to sufficiently early.

Along with environmental exposures, inborn factors, nutrition, other diseases or injury, socio-economic status and age-sex dependent factors are major variable clusters in human carcinogenesis. For many forms of cancer, smoking adds another critical variable. Epidemiological evaluation requires consideration of a sufficiently complete set of variables and in the appropriate form. Path diagrams are shown to be a useful device to compare completeness of variable sets.

Path analysis originally proposed by Sewall Wright for statistical genetics (Li) and recently applied to sociology (3),(4), has been proposed for application to chronic disease epidemiology. Path analysis describes an adaptation of multivariate analysis in which, either on an a priori basis, or as a result of partial correlation analysis, the roles of "independent" (measured) and exogenous (unmeasured) variables are structurally ordered in relationship to dependent variables, in this case, incidence rates of cancer. Path analysis methods are currently being tested for their appropriateness in environmental cancer epidemiology. They appear to have the desirable feature of being able to partial out the contributory role of a multiplicity of factors, but the assumptions needed may restrict their applicability.

Evaluation of the role of air pollution in respiratory cancer is based on four types of findings:

- that inhaled materials of various types can and do lead to increased lung cancer rates,
- that carcinogenic agents are found in polluted air,
- that there is an urban excess of lung cancer,
- differential effects of migration of populations on lung cancer rates.

The conclusion hinges on judgment concerning the principal arguments supporting and opposing the causal role of air pollution in the urban excess of lung cancer. While the weight of evidence now available does not support the conclusion that air pollution is an important causal factor, neither can the possibility be dismissed.

In the case of ingested asbestos and the possible role it may have in cancer of the gastro-intestinal tract, the following findings need to be considered:

- there is epidemiological evidence that gastro-intestinal cancer rates are elevated in groups occupationally exposed to asbestos.
- asbestos fibers and fibrils can be found in water and some foods.
- although asbestos minerals can enter water both from natural and technogenic sources, the associations between asbestos levels in water (or probable differences in such levels) and gastro-intestinal cancer rates have not yet been systematically examined; neither is uptake from ingested asbestos well understood.
- a few orally ingested agents have been shown to be carcinogenic for man.

Other types of evaluation are that of arsenic in water (6) or air (7) based on estimates of body burden, and that of nitrate in water (8) based on an association with increased methemoglobin in infants. These agents, for which a carcinogenic potential is suspected, are being assessed and controlled on the basis of non-malignant responses.

Among the factors to be considered in evaluating human carcinogens are:

- distribution of exposures in time and place
- number of people at risk
- available information and its validity concerning exposures, responses (carcinogenic or not) and other relevant variables.
- adequacy of model and data with respect to completeness of variable set and variable representation.
- adequacy of epidemiological strategy and of statistical analysis.
- ease of preventing hazardous exposure
- potential availability of additional data

- the nature of other health reactions to the agent(s).

A satisfactory strategy for environmental cancer control depends on:

- realistic models of exposure including evaluation of effects of non-environmental variables,
- suitable population studies, with special attention to occupationally exposed groups
- study and inferences based on non-malignant responses to carcinogenic exposures, such as body burden estimates, cytological changes, and metabolic responses,
- utilization of a consistent set of principles for evaluation and
- appropriate applications of the results of evaluation.

In light of experience with asbestos, vinyl chloride, benzo(a)pyrene, arsenic, and beryllium, as community pollutants, the study of non-malignant responses to possible carcinogens should have a prominent place in such a strategy.

1. J. Higginson and L. Tomatis, "Industrialization, Cancer Incidence and Possible Prevention", Proc. XVI, Int. Cong. occup. Health, Tokyo, 246-250, 1971

2. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, vol. 1 (1972), vol. 2, (1973), vol. 3 (1973), vol. 4 (1974) and vol. 5 (1974).

3. D. R. Heise, "Problems in Path Analysis and Causal Inference" in Sociological Methodology, (1969), E. F. Bergetta and G. W. Bohrnstedt (Ed) Jossey-Bass, San Francisco.

4. K. C. Land, "Principles of Path Analysis", op.cit.

5. J. R. Goldsmith and K. Berglund, "Epidemiological Approach to Multiple Factor Interactions in Pulmonary Disease: The Potential Usefulness of Path Analysis", Proc. N.Z. Acad. Science, 221, 361-375, 1974.

6. J. R. Goldsmith, M. Deane, J. Thom, and G. Gentry "Evaluation of Health Implications of Elevated Arsenic in Well Water", Water Resch., 6, 1133-1136, 1972.

7. S. Milham, Jr. and T. Strong, "Human Arsenic Exposure in Relation to a Copper Smelter", Environ. Res., 7, 176-182, 1974.

8. L. A. Shearer, J. R. Goldsmith, C. Young, O.A. Kearns, and B. R. Tamplin, "Methemoglobin Levels in Infants in an Area with High Nitrate Water Supply", Am. J. Public Health, 62, 1174-1180, 1972.

RECHT

Dans le domaine de la protection de l'homme et de l'environnement, les critères sont définis habituellement comme les relations entre l'exposition d'une cible à une pollution ou nuisance et le risque et/ou l'ampleur de l'effet défavorable ou indésirable qui en résulterait dans des circonstances données. Il est souhaitable que cette relation soit quantitative et que, notamment, l'exposition soit exprimée sous forme de valeurs numériques, de concentration, d'intensité, de durée ou de fréquence. Le risque est lui-même défini comme une probabilité d'apparition d'effets défavorables ou indésirables résultant d'une exposition donnée à un ou plusieurs polluants ou nuisances pris isolément ou en combinaison. Le risque et l'effet défavorable ou indésirable doivent, autant que possible, être exprimés d'une manière précise.

La recherche et l'établissement de ces critères représentent pour les autorités responsables de décisions règlementaires et administratives un élément de jugement et une base scientifique de réflexion et de décision. Idéalement, les critères devraient être proposés avant qu'une réglementation ne soit mise en oeuvre pour réduire les pollutions et ou les nuisances. En raison même de son objectif, l'établissement de critères est une entreprise étendue et souvent malaisée; elle doit affronter de nombreuses difficultés dont les unes sont liées aux premiers termes de la relation, c'est-à-dire l'exposition, et dont les autres concernent le risque ou l'effet défavorable. Il y a d'abord le grand nombre de polluants à considérer, la variété des facteurs physico-chimiques intervenant dans l'exposition, la diversité des voies par lesquelles l'homme peut être touché, l'absence de données chiffrées et comparables sur l'état de la pollution du milieu, la présence simultanée dans l'air inhalé ou dans l'eau et les aliments ingérés, de nombreux polluants ayant des actions synergiques ou antagonistes. Il y a, en outre, la complexité des processus métaboliques et biochimiques intervenant dans la contamination ou dans l'atteinte humaine, la définition du caractère défavorable ou indésirable de l'effet ou la nature du risque à considérer, l'interprétation des données. Deux éléments importants doivent retenir l'attention et concernent d'une manière directe un des buts essentiels de la protection contre le danger des pollutions et nuisances; ils constituent d'ailleurs des impératifs majeurs dans la recherche des critères. Il y a d'abord le fait que les concentrations caractérisant l'exposition sont, en général, relativement basses et variables dans le temps et selon les régions. Il s'agit par ailleurs d'une exposition chronique à laquelle ne s'appliquent pas nécessairement les expériences acquises lors d'accidents aigus de pollution ou les données de l'hygiène industrielle. Si pour certains polluants, on peut retenir une relation linéaire dose/effet, elle n'est pas démontrée, ni même démontrable pour un grand nombre d'autres polluants en considérant des effets déterminés. Le caractère de la population dans son ensemble doit être pris en considération; la population comprend des groupes d'individus non homogènes, dont l'âge et les conditions sanitaires sont différents et parmi lesquels nous trouvons des enfants, des vieillards, des femmes enceintes et des malades.

Fréquement, dans l'interprétation des résultats des facteurs concomitants apparaissent, qui n'ont rien à voir avec le polluant considéré et créent certaines perturbations (par exemple: tabac, médicaments, alimentation, habitudes sociales, etc...). Un des problèmes fondamentaux de la pathologie spéciale de l'environnement est la difficulté de qualifier d'indésirable ou de défavorable un effet sur la santé humaine. En raison du niveau relativement bas des expositions, les effets à prendre en considération appartiennent au domaine des effets "subcliniques"; ils ne sont pas nettement pathologiques. Les signes indiquant l'atteinte sont rarement pathognomoniques et beaucoup d'entre eux ne sont révélés que par des études statistiques. La radioprotection et l'hygiène industrielle nous avaient habitués à une certaine signification dans l'application de modèles métaboliques établis selon les caractéristiques de l'homme standard.

Faut-il un ou plusieurs critères est une question qui peut être posée et constitue certainement un problème intéressant à discuter. Pour les autorités responsables des décisions en matière d'environnement, il est plus commode de n'avoir à considérer qu'un seul critère. On peut, dans ce cas, fixer le niveau à partir duquel le premier effet défavorable apparaît; un exemple est l'oxyde de carbone. On sait qu'à partir de 4% de carboxyhémoglobine il y a un effet défavorable certain sur l'appareil cardio-vasculaire du à l'hypoxie des tissus: à partir de 2% il y a une interférence avec les performances d'exercices physiques chez les malades cardio-vasculaires. On sait aussi que l'intensité de l'effet augmente avec l'exposition et qu'en outre d'autres effets défavorables (système nerveux arthérosclérose, foetus) peuvent intervenir. Pour le dioxyde de soufre et la fumée, on sait par les études épidémiologiques qu'à partir d'une concentration de 250 $\mu g/m^3$ de SO_2 associée à des concentrations plus faibles de fumée, il y a un effet défavorable et significatif du point de vue sanitaire sur l'appareil respiratoire; mais vu la difficulté de fixer à l'heure actuelle des limites précises, on a été amené à présenter d'autres relations dose/effet à des seuils inférieurs ou supérieurs d'exposition et liés à des atteintes ou à des risques d'atteintes exprimés en général d'une manière assez vague. Dans le cas particulier de ces polluants, une série de critères se justifie et laisse aux autorités sanitaires le soin de décider en tenant compte des considérations sociales ou même économiques, quel est le critère à considérer dans l'établissement de normes.

Un troisième exemple qui peut illustrer les difficultés est celui du plomb et de l'imprégnation saturnine des populations. Les voies par lesquelles l'homme se contamine sont nombreuses (inhalation, ingestion, peau). Les sources de contamination varient notamment selon les régions et les habitudes alimentaires. Néanmoins, on peut reconnaitre que la plombémie ou la mesure de l'ALAD représentent des indicateurs précieux de l'imprégnation saturnine globale humaine. A partir de certains taux de plombémie, il apparaît une atteinte de l'enzyme intervenant dans la synthèse de l'hème. Une atteinte significative de cette enzyme est géneralement considérée comme indésirable et peut être liée à un taux de plombémie relativement précis. Le groupe le plus sensible est celui des enfants; dès lors, dans le critère, la plombémie des enfants devient le facteur déterminant. En partant de ce critère, que l'on pourrait qualifier de fondamental, on peut "dériver" des normes pratiques concernant certaines voies de contamination de l'homme. S'il est prouvé que l'appareil respiratoire peut représenter l'organe critique dans le cas d'une contamination humaine par inhalation, on peut établir un deuxième critère, qui est la relation entre une concentration du plomb dans l'air et un effet déterminésur l'appareil respiratoire ou certains de ses mécanismes de défense (macrophages).

D'autres exemples pourraient être apportés confirmant qu'on ne peut ériger en règle absolue la fixation d'un seul critère et, qu'au contraire, un ensemble de relations correspond mieux à l'état actuel des connaissances scientifiques. Il est évident que, dans ce cas, chaque critère doit être assorti de commentaires explicatifs qui puissent permettre aux autorités responsables des décisions d'en comprendre la portée et la signification réelle.

Quant au problème des groupes de population à protéger, l'analyse précédente révèle qu'en raison de la non homogénéité de la population il faut prendre en considération un groupe de population sensible mais significatif et représentatif. Dans le cas des enfants et de la contamination par le plomb, le problème est simple car il s'agit d'un groupe important de la population et constitué d'individus bien portants.

Quand le groupe identifié comme sensible est composéd'individus malades, le problème est plus complexe et plus délicat; par exemple, le monoxyde de carbone à partir de 4% de saturation de l'hémoglobine a une action certaine sur l'appareil cardio-vasculaire surtout chez les individus présentant déjà des anomalies ou considérés comme individus "à risque". Il ne s'agit pas en fait de malades hospitalisés mais d'individus relativement nombreux dans la population actuelle et qui, à partir d'un certain âge, sont susceptibles de présenter un accident cardio-vasculaire. Il est raisonnable dans ce cas de baser une décision normative éventuelle sur un groupe représentatif et significatif du point du vue démographique. Mais on sait également que le monoxyde de carbone peut avoir, même en dessous de 2% de saturation, une action sur des malades dont l'état de santé est particulièrement déficient au point de vue cardio-vasculaire ce sont les malades "in extremis" dont il a été fait référence dans le rapport technique 506 de l'OMS. Vu la très grande fragilité de ces malades, on pourrait arriver à la conclusion que même une légère augmentation du COHb par rapport aux niveaux d'origine endogène constituerait un risque. Est-il raisonnable, dans un programme de réduction des nuisances, de baser une

décision sur un critère aussi sévère? Le problème reste ouvert et peut, sans aucun doute, constituer une question importante à discuter.

Criteria for the protection of man and the environment are normally defined as the relation between the exposure of a target to a pollutant or nuisance and the risk or magnitude of a harmful or undesirable effect which would result under specified circumstances. This relationship should preferably be quantitative, and in particular the exposure level should be expressed as a numerical value, in terms of concentration, intensity, duration or frequency. The risk itself is defined as the expected frequency of harmful or undesirable effects arising from a given exposure to one or more pollutants or nuisances, considered alone or in combination. The risk and the harmful or undesirable effect must be expressed in as precise a manner as possible.

For the authorities responsible for legislative and administrative decisions, the search for and establishment of such criteria provide a means of evaluation and a scientific basis for consideration and decision. Ideally, these criteria should be put forward before standards are instituted for the reduction of pollution of nuisances. By reason of its aim, the establishment of criteria is a far-reaching and often difficult task; there are many difficult points to be considered, some of which are connected with the first part of the relationship, namely, exposure, and others with the risk or harmful effect. First, there is the enormous number of pollutants to be considered, the diversity of physico-chemical factors involved in exposure, the many different ways in which man may be affected, the absence of comparative numerical data on the state of environmental pollution and the presence at one and the same time in air inhaled or food and water ingested of numerous pollutants having synergistic or antagonistic effects. There is in addition the problem of the complex nature of the metabolic and biochemical processes involved in contamination and in the effect on man, the definition of the harmful or undesirable nature of the effect or the character of the risk under consideration and the interpretation of the data. Two significant factors merit attention and are directly concerned with one of the essential aims of protection against the dangers of pollutants and nuisances; what is more, they amount to major essentials in the search for criteria. First, there is the fact that concentrations involved in exposure are, in general, relatively low and vary according to weather and district. We are dealing, moreover, with chronic exposure, to which experience obtained on the occasion of acute accidents arising from pollution, or the findings of industrial hygiene, do not necessarily apply. Although for certain pollutants a linear dose/effect relationship may be accepted, it has not been proved, and indeed cannot be proved for a large number of other pollutants, as regards given effects. The characteristics of the population as a whole must be taken into consideration, and it is composed of heterogeneous groups of individuals of different ages and states of health, amongst whom we find children, the aged, pregnant women and diseased persons.

In interpreting results we frequently come across concomitant factors which are unconnected with the pollutant under consideration and which cause certain complications (for example: tobacco, medicines, food, social habits, etc....). One of the fundamental problems of special environmental pathology is the difficulty of classifying an effect on human health as undesirable or harmful. Because of the relatively low exposure rate the effects to be considered are 'subclinical' - that is, they are not clearly pathological. The signs indicative of an injurious effect are rarely pathognomic and many of them become evident only through statistical studies. Radiation protection and industrial hygiene had previously accustomed us to attributing a certain significance in practice to metabolic models based on the characteristics of the average man.

We may ask whether we need one or several criteria, and the problem is certainly an interesting one. For the authorities responsible for making decisions in environmental matters it is more convenient to have only one criterion to consider. Thus one may establish the level at which the first harmful effect appears; carbon monoxide provides one example. We know that, starting at a carboxyhaemoglobin level of 4%, there is a definite harmful effect on the cardiovascular system, owing to hypoxia of the tissues. We know also that the intensity of this effect increases with exposure and that in addition other harmful effects may occur (affecting the nervous system or the foetus or in the form of arteriosclerosis). For sulphur dioxide and smoke we know through epidemiological surveys that above a concentration of 250 $\mu g/m^3$ of SO_2 associated with 150 $\mu g/m^3$ of smoke a significant injurious effect develops threatening the health of the respiratory organs; but owing to the difficulty of determining precise limits at the present time, other dose/effect relationships have been prepared involving higher or lower exposure limits and connected with injurious effects, or the risk of such effects, expressed generally speaking in rather a vague way. In the individual case of this pollutant, the adoption of a series of criteria is justified, the health authorities being left to decide, having regard to social or even economic considerations, what criterion is to be taken into account in laying down standards.

A third example which may illustrate the difficulties is that of lead and its concentrations in the population. The ways in which man may become contaminated are numerous (inhalation, ingestion, skin). The sources of contamination vary in particular according to district and feeding habits.. Nevertheless, it is true that the blood-lead level or the ALAD level are valuable indicators of the aggregate lead-contamination level in man. Above certain blood-lead levels, the enzyme responsible for haem synthesis is damaged. A significant effect is generally considered to be undesirable and may be linked with a *relatively precise level. Children constitute the most sensitive group. For this reason the blood-lead level in children is the determining factor in the criterion. On the basis of this parameter, which may be described as fundamental, it is possible to work out practical criteria or norms with regard to certain ways in which man becomes contaminated. If it is proved that the respiratory system may represent the critical organ in the case of human contamination by inhalation, a second criterion may be elaborated, namely the relationship between a given concentration of lead in the atmosphere and the measured effect on the respiratory system or on certain of its defence mechanisms (macrophages).*

Other examples might be cited showing that it is impossible to lay down a single criterion in the form of an absolute rule, but that on the contrary a group of relationships corresponds more accurately to the present state of scientific knowledge. It is evident that in such circumstances each criterion must be accompanied by explanatory notes allowing the authorities responsible for taking decisions to understand its true scope and meaning.

On the question of the groups of persons to be protected, the foregoing analysis shows that in view of the heterogeneous nature of the population it is necessary to consider groups which are not only at risk but also significant and representative. In the case of children and contamination by lead, the problem is simple, since we are concerned with a significant group of the population composed of healthy individuals. If the group identified as being at risk is composed of diseased persons, the problem is both more complex and more delicate: for example a saturation level of carbon monoxide in haemoglobin exceeding 4% has a definite effect on the cardiovascular system, especially in individuals already displaying anomalies or viewed as being 'at risk'. We are not concerned with patients in hospitals but with the fairly numerous individuals in the present-day population who, above a certain age, have a tendency to cardiovascular accidents. In such a case it is reasonable to base any legislative decision on a group which is demographically representative and significant. But we also know that carbon monoxide, even below 4% saturation, may have an effect on diseased persons whose health is particularly deficient as regards the cardiovascular system. These are the patients 'in extremis' referred to in No. 506 WHO Technical Report. In view of the very delicate condition of such patients, one might argue that even a slight increase in the COHb above their original endogenous level would constitute a risk. Is it reasonable, in a programme dealing with the reduction of nuisances to base a decision on so strict a criterion? The question still remains unanswered, and can without doubt provide an important subject for discussion.

TREMOLIERES

Pour juger des effets de la santé de la pollution de l'environnement, un grand vide subsiste: le flou, voire l'absence d'une méthodologie permettant de transposer à l'homme les travaux expérimentaux sur l'animal; ceci aussi bien pour classer qualitativement les polluants, que pour fixer quantitativement la dose journalière acceptable.

Le Comité "Contamination de la Chaîne Biologique" du Ministère de l'Environnement français a établi, sous le nom de "toxicologie métabolique", une méthodologie dont l'objet est d'établir pour les substances étrangères les processus de métabolisation maintenant établis pour les nutriments, suivant les espèces, les états de nutrition, les développements, les associations de toxiques.

Sous-jacente aux études de toxicologie aigue,subaigue ou chronique, des toxicités de relais, des pouvoirs cancérigènes et tératogènes, qui restent des guides indispensables, la toxicologie métabolique s'efforce d'expliquer les mécanismes des faits observés. Elle comporte:

- la physiologie de la diffusion et de la transformation par les divers tissus suivant les doses et les associations;
- les systèmes enzymatiques détoxiquants (oxydases, peroxydases, etc....);
- les répercussions de ces systèmes sur les métabolismes de la bioénergétique et des biosynthèses nucléiques, protéiques et membranaires;
- les effets physiologiques et pharmacodynamiques sur les divers organes du produit et de ses métabolites suivant l'état nutritionnel et métabolique du récepteur.

ABSORPTION - DIFFUSION - CONCENTRATION - ELIMINATION

Il faut étudier suivant les condition d'ingestion:

- le sort du composé dans le tube digestif et son absorption. On devra approfondir le role:

- oo de la flore digestive (exemple: les cyclamates sont complément métabolisés par la flore intestinale de certains individus seulement, aussi bien dans l'espèce humaine que chez le lapin New Zealand),
- oo des mucus digestifs, les modes de transport à travers l'entérocyte, l'intervention des tissus lymphoides de la sous-muqueuse intestinale, de cellules de Küpffer, des macrophages, comme barrières successives possibles,

o la répartition et les possibilités d'accumulation dans les divers tissus: ceci pose le problème des techniques d'identification, de détection et de dosage du composé et de ses éventuels dérivés dans les substances biologiques comportant les chélates protéines métaux.

Il faut prévoir un travail de chimie organique pour la préparation de substances étalons,

o l'excrétion dans la bile, les fèces, l'urine, l'air expiré.

METABOLISATION du TOXIQUE à L'ECHELON CELLULAIRE

Suivre le passage d'un composé à travers l'organisme implique donc la reconnaissance de son métabolisme par les divers tissus. Quels dérivés sont produits? Dans quels tissus?

A. *Systèmes enzymatiques de détoxication ou de Transformation*

On est donc tout naturellement amené à la recherche et à l'étude des voies enzymatiques qui assurent la transformation du composé. Bien entendu le résultat d'une telle recherche peut être négatif. Exemple: la thalidomide subit une transformation spontanée, sans intervention enzymatique. Il faut aussi faire une place :a part aux enzymes de la flore intestinale.

Enfin, le composé peut etre excrété inchangé. Ou bien encore, les divers processus peuvent jouer simultanément.

On sait que les transformations métaboliques des composés étrangers ont lieu dans les reins, le poumon et surtout dans le foie; mais le tissu adipeux pourrait aussi jouer un rôle ainsi aue la muqueuse intestinale. Les réactions ont lieu en deux phases:

- o phase I :oxydations, réductions, hydrolyses
- o phase II :synthèses, réactions de conjugaison

Les enzymes de la phase I sont localisßees dans les microsomes.

On les appele en anglais "processing enzymes" ou "drug metabolizing enzymes". Ces processus n'aboutissent pas forcément à la détoxification de la molécule "traitée".

On s'attachera :a reconnaître:

- o quelles sont ces enzymes;
- o dans quelles conditions physico-chimiques agissent-elles? Ce qui revient à explorer leur environnement: entre autres, ces enzymes nécessitent la présence de plusieurs co-facteurs, notamment NADPH, Cytochrome P450, etc. Les mécanismes de transmission des électrons du substrat à l'oxygène posent d'ailleurs de difficiles problèmes, étant donné la multiplicité des co-facteurs intermédiaires dont le rôle est mal connu;
- o dans quelles conditions physiologiques agissent-elles? En d'autres termes, peut-on mettre en évidence un induction ou une répression de la synthèse de ces enzymes dans différentes conditions expérimentales ou physio-pathologiques.

B. *Les effets du composé et de sa métabolisation sur les métabolismes cellulaires*

Le comportement physiologique et biochimique de l'animal soumis à un traitement à long terme devra être examiné le plus finement possible sous son double aspect: comportement habituel, comportement en réponse à une stimulation (jeûne, autre nuisance ou déséquilibre nutritionnel, etc...).

- On présentera un profil descriptif de l'animal:
    - étude de la croissance, des ingesta et du rendement alimentaire;
    - échanges respiratoires, dépenses d'énergie et d'azote;
    - état hormonal (insulinémie, corticostéronémie, etc.)
    - poids des différents organes et composition corporelle, études histologiques, exploration fonctionnelle, etc...).
- On évaluera les techniques habituelles comportant l'emploi de traceurs radioactifs: les vitesses de renouvellement des acides nucléiques, des protéines, des phospholipides dans les divers tissus.
- On déterminera les activités enzymatiques potentielles de certaines voies métaboliques.
- L'étude cinétique des concentrations des métabolites et des co-facteurs dans un tissu, soit sur l'animal entier, soit sur des organes, tissus ou organites, est particulièrement intéressante pour révéler les différences de comportement métabolique et proposer des hypothèses sur les mécanismes d'action des composés dans un tissu.

LES CONDITIONS EXPERIMENTALES

La plupart des expérimentations reposent sur des animaux bien nourris et toujours soumis à un seul facteur: l'agent ou'on veut étudier. Or les résultats concernant des sujets sains ne s'appliquent pas forcément à ceux dont le métabolisme est déjà "biaisé". Il y aurait intérêt à reprendre les études décrites chez des animaux en état d'obésité nutritionelle, diabétiques, etc., ou recevant un régime carencé en protéines, en diverses vitamines, ou riche en alcool éthylique ou en saccharose. De telles manipulations rapprocheraient les modèles expérimentaux de certaines conditions qui sont réalisées dans l'espèce humaine par des conditions de vie particulières. On sait par exemple que les "processing enzymes" sont inhibés par l'intoxication chloroformique, la castration, la dénutrition, la thyroxine, la morphine; induits par les barbituriques, les hydrocarbures polycycliques et diverses classes de stéroïdes comme les androgènes, les glucocorticoïdes, les anabolisants, les organochlorés, etc.

Les problèmes de toxicologie métabolique se posent en termes particuliers lors du développement.

- o Au cours de la vie foetale:
  - oo action du toxique administré expérimentalement directement au foetus sur son développement général et sur certains aspects non "recupérables" ultérieurement du développement: différenciation sexuelle, différenciation du système nerveux central;
  - oo passage transplacentaire du toxique.
- o Au cours de l'allaitement:
  - oo passage de la substance toxique dans le lait.
- o Au cours de développement.

CONCLUSION

Il s'agit:

- o d'affermir les bases d'une méthodologie de

l'évaluation toxicologique;

- **d'élaborer pas à pas une nomenclature permettant de classer les polluants suivant leurs effets métaboliques;**
- **de développer une approche pluridisciplinaire, analogue à celle qui a élabore la physiologie des métabolismes en nutrition.**

There is a great gap in our knowledge for assessing the effects of environmental pollution on health, namely, the vagueness or indeed the absence of a methodology for extrapolating animal experiments to man, both for the qualitative classification of a given element in pollutants and for the quantitative assessment of the acceptable daily dose.

The French Ministry of the Environment's Committee on the Contamination of the Biological Chain has elaborated a methodology under the name of 'Metabolic Toxicology', which aims to determine, for foreign substances, the processes of metabolization which have now been determined for nutrients, according to species, state of nutrition, growth and associations of toxins.

Underlying the studies of acute, sub-acute or chronic toxicology, relayed toxicity, carcinogenicity and teratogenicity, which remain invaluable guides, metabolic toxicology attempts to explain the workings of observed facts. It involves:

1. *The physiology of diffusion and transformation by various tissues, according to dose and associations;*
2. - *detoxicating enyzme systems (oxidases, peroxidases, etc.);*
   - *the effects of these systems on the matabolisms of bioenergetics and of nucleic, proteinic and membrane biosynthesis;*
3. *The physiological and pharmacodynamic effects of the product and its metabolites on the various organs in relation to the nutritional and metabolic state of the subject.*

I. - ABSORBTION - DIFFUSION - CONCENTRATION - ELIMINATION

The following must be considered, according to the circumstances of ingestion:

- *what happens to the compound in the alimentary* canal, and its absorption.

We must further investigate the role of:

- digestive flora (for example: cyclamates are completely metabolized by the intestinal flora of certain individuals only, both in man and in the New Zealand rabbit),
- digestive mucus, the manner of passage through the enterocyte, the action of the lymphoid tissues of the intestinal submucosoe, Küpffer cells and macrophages as possible successive barriers.
- distribution and the chances of accumulation in the various tissues: this poses the problem of techniques for identifying, detecting and measuring concentrations of the compound and of any derivatives in biological substances containing metallic protein chelates.

A research project in organic chemistry will have to be undertaken to establish standard substances:

- excretion in the bile, faeces, urine and exhaled air.

II. - METABOLIZATION OF TOXIN AT CELL LEVEL

Following the progress of a compound through the organism implies ascertaining its metabolization by the various tissues. Which derivatives are produced, in which tissues?

A. Enzymatic detoxication or transformation systems

We thus come quite naturally to studying and carrying out research into the enzyme processes responsible for the transforming of the compound. The results of such research might of course be negative; for example, thalidomide undergoes spontaneous change without the action of enzymes. Enzymes in the intestinal flora must be considered separately. Finally, the compound may be excreted unchanged or, again, the various processes may take place simultaneously.

We know that metabolic transformation of foreign compounds takes place in the kidneys, the lungs, and above all the liver; but adipose tissue and the intestinal mucosa might also be involved. Reactions take place in two stages:

stage I : oxidation, reduction, hydrolysis
stage II : synthesis, conjugation reactions.

The enzymes involved in stage I are localized in the microsomes. They are called 'processing enzymes' or 'drug-metabolizing enzymes'. These processes do not necessarily result in the detoxification of the molecule subjected to processing.

We shall try to discover:

- o *which these enzymes are;*
- o *under what physico-chemical conditions they operate. This amounts to investigating their environment; amongst other things, these enzymes require the presence of several other cofactors - in particular NADPH, cytochrome P 450, etc. Moreover, mechamisms by which electrons are transferred from substrate to oxygen present difficult problems in view of the many intermediate cofactors, whose role is not well understood;*
- o *under what physiological conditions they operate. In other words, can we show that the sythesis of these enzymes is either stimulated or inhibited by different experimental or physiopathological conditions?*

B. The effects of the compound and its metabolization on cell metabolism

The physiological and biochemical reactions of an animal subjected to long-term treatment must be observed as closely as possible both for normal reactions and for reactions in response to a stimulus (starvation, other dietary disturbances or imbalances, etc).

a) an outline of the animal's condition will be given, covering:
- *study of growth, ingesta, nutritional efficiency;*
- *respiratory exchange, expenditure of energy and nitrogen;*
- *hormone level (insulinaemia, corticosteronaemia, etc..);*
- *weight of the various organs and physical composition (histological study, functional examination, etc).*

b) An evaluation will be made of the usual techniques using radioactive tracers,ie. rate of renewal of nucleic acids, proteins and phospholipids in the various tissues.

c) The potential enzyme activity of certain metabolic processes will be determined.

d) The kinetic study of metabolite concentrations and cofactors in a tissue, either in the whole animal or in certain organs, tissues or organs is of particular value for detecting differences in metabolic action and for putting forward hypotheses on the ways in which compounds act in a tissue.

III. - EXPERIMENTAL CONDITIONS

The majority of experiments are carried out on well-nourished animals which are subjected to one factor only, namely, the factor to be investigated. Results obtained for healthy subjects are not necessarily applicable to those whose metabolism is already in a state of imbalance. It would be interesting to repeat the experiments described in the case of animals which are obese due to diet, diabetic, etc., receiving a low-protein diet or a diet deficient in certain vitamins, or one with a high ethyl alcohol or saccharose content. Such variable conditions would approximate to experimental models for certain conditions induced in man by certain conditions of life. We know, for instance, that 'processing enzymes' are inhibited by barbiturates, polycyclic hydrocarbons and various types of steroids such as androgens, glucocorticoids, anabolizing agents, organochlorinated substances, etc. The problems of metabolic toxicology are particularly apparent during development.

a) During foetal life:
- effect of the toxin experimentally administered directly to the foetus on its general development and on certain irreversible aspects of development such as sexual differentiation, differentiation of the central nervous system;

- transplacental transfer of toxins;

b) During lactation:
- transfer of the toxic substances in milk.

c) During further growth.

CONCLUSION

1. The foundations of a methodology for toxicological evaluation must be firmly laid.

2. A nomenclature should be worked out step by step making it possible to classify pollutants according to their effects upon metabolism.

3. *A multidisciplinary approach should be used similar to that adopted in charting the physiology of nutritional metabolisms.*

An expanded and accelerated WHO programme on environmental health criteria, stressing the need for an integrated approach, was developed in 1972. In response to a number of World Health Assembly Resolutions (2) and recommendations of the United Nations Conference on the Human Environment (3), a WHO Scientific Group was convened in April 1973 to examine the scientific basis of the proposed programme (4). The programme is being implemented in close collaboration with national institutions and WHO collaborating centres, and has the following objectives:

- establishment of health criteria for environmental quality, and provision of guidelines for the setting up of exposure limits to protect man's health,
- promotion of research relevant to the development of environmental health criteria,
- identification of new environmental hazards to public health.

The following topics are briefly discussed in this contribution to the plenary discussion group on the scientific data base required for decisions to protect human health: o definition of environmental health criteria as used in the WHO programme, o shortcoming of the existing knowledge on exposure/health effect relationship, o the concept of a threshold for biological effects of environmental hazards, o the progress made in the preparation of the WHO criteria document and the identification of new or potential hazards.

Definition of environmental health criteria

Ideally, environmental health criteria may be defined as complete sets of quantitative exposure/response relationships for all environmental factors, involving different effects and different population groups, and covering the whole range of anticipated exposure levels (1). This relationship has not been totally defined for any single agent and less for combinations of agents and factors in the environment, although studies on ioniying radiation have come close to meeting the situation for practical purposes.

Health effects of environmental agents

Linking environmental exposure to prompt effects (i.e. those appearing relatively soon -- within days or weeks after exposure) such as acute disease or death, is usually much less difficult than associating the exposure with chronic disease, which may be a very subtle effect and often not detectable except with statistical methods applied to comparatively large human populations. In addition to the characteristics of exposure (intensity, frequency, variability, rate, duration), the biological response depends on a variety of host factors. Some population groups such as the young, the old, the sick or debilitated may be particularly susceptible to environmental factors. An exposure that would have no effect on a normal adult individual could aggravate the course of a chronic illness, e.g. cardio-vascular or respiratory disorders. This susceptibility may be temporary or permanent, inherited or acquired. The presence of factors other than those under consideration and their interactions may significantly and profoundly modify the response to a given environmental agent.

It is obviously unsatisfactory to await the occurrence of episodes of high or accidental pollution, with their associated adverse health effects, as a means of identifying environmental hazards; a detailed study of such occurrences is, however, of great value particularly when an exposure-effect relationship can be established. The primary basis for environmental health criteria and exposure limits will have to be the experimental work done in the laboratory before human injury has occurred. Nevertheless such experimental work must be supplemented by epidemiological clinical and toxicological programs that seek to identify indices of adverse biological effects in man, for there is wide variability in human response. Man does not necessarily respond in a manner predicted by animal experimentation, where variability in the response of different species and strains also exists.

Exposure limits

An important concept for the establishment of exposure limits is the threshold of response, i.e. the exposure level below which no demonstrable effects occur. It may be difficult to prove or disprove experimentally the existence of a true threshold for certain environmental agents and certain effects. Effects which appear not to have a threshold occur in independent cells, in cell cultures, or in circumstances in which affected cells are able to react autonomously or when repair processes are not effective.

There are some experimental data indicating that there may not be a demonstrable threshold for mutagenesis but for other effects on reproductive processes it is assumed that threshold levels exist. Since it has not been possible to reach agreement as to whether there is a threshold for chemical carcinogens and, if it exists, how to determine it (5),some authorities consider it prudent to extrapolate exposure-response curves to zero by a straight line.

For some environmental factors (e.g. temperature, essential elements) there is an optimal level of exposure, and departure from this level, in either direction, positive or negative, may cause unfavorable biological effects.

The general principle to be followed in setting-up the exposure limits for effects other than mutagenesis or carcinogenesis is that the limit should be set in all cases below the "no-adverse effect level" i.e. below the exposure level at which no pathological effects or physiological or biochemical impairment has been demonstrated (4) and that the population group in which the effects are likely to occur be kept as small as possible. The practical application of this principle is difficult because of disagreement as to what constitutes physiological or biochemical impairment. This brings us to the problem of the sensitivity of the tests used to identify such impairment, and to the meaning to be attached to a statistically significant departure from the "normal" state of the organism.

Interactions

A most important and difficult consideration in establishing exposure limits is the possibility of interactions among various environmental factors. Of these, synergism-the exaggeration of the effect considerably beyond the additive-- presents the greatest problem in determining safe exposure levels. The interactions may have important effects on the exposure/ response relationships, though they may be observed only at certain exposure levels, while at very low exposures there may be no evidence of synergism or antagonism.

Interactions among physical, chemical and biological factors take place against a background of social, cultural and economic factors in the community, which may influence the pattern and intensity of environmental interactions, so that consideration of the entire complex situation is fundamental to an understanding of events and to achievement of control. Only by considering man in the context of his total, multifactorial environment can we hope to attain that state of health that is not merely the absence of disease but complete physical, mental and social well-being.

Risk/benefit evaluation

To permit wise steps to be taken towards legislative control of hazardous substances in man's environment, it is essential to make a very careful evaluation of risks and benefits, but this may be extremely difficult.

The expertise needed for the evaluation of risk is different from that needed for benefit evaluation. When evaluating the risk, concern is focused on adverse health effects on man, damage to the environment, and misuse of natural resources. On the benefit side, the emphasis is on value to the consumer and the country, i.e. improvement in the health of the population and the availability of cheaper and better products, particularly those that modern man considers indispensable. Economic considerations, such as the improvement of productivity, the development of resources, or a better balance of trade are also important. It should be noted that very often the population group which is exposed to the risk is not the same as the population group which may have the benefits from a given environmental situation.

In both types of evaluation consideration must be given to the consequences that could arise from a regulatory action. It is possible that the remedy may prove to have worse consequences than the evil it was intended to cure(6).

WHO environmental health criteria programme

The priority environmental pollutants and hazards for which WHO criteria documents or preliminary reviews will be prepared have been selected taking into account the following considerations(4):

"o Severity and frequency of observed or suspected adverse effects on human health. Of importance are irreversible or chronic effects, such as genetic, neurotoxic, carcinogenic, and embryotoxic effects including teratogenicity. Continuous or repeated exposures generally merit a higher priority than isolated or accidental exposures.

o Ubiquity and abundance of the agent in man's environment. Of concern are inadvertently produced agents, the levels of which may be expected to increase rapidly, and agents that add to a natural hazard.

o Persistence in the environment. Pollutants that resist environmental degradation and accumulate, in man, in the environment, or in food chains deserve attention.

- Environmental transformations or metabolic alterations. Since these alterations may lead to the production of chemicals that have greater toxic potential, it may be more important to ascertain the distribution of the derivatives than that of the original pollutant.
- Population exposed. Attention should be paid to exposures involving a large portion of the general population, or occupational groups, and to selective exposures of highly vulnerable groups represented by pregnant women, the newborn, children, the infirm, or the aged".

Using these considerations, a priority list of some seventy chemical, biological and physical agents was prepared (4). Environmental agents for which criteria documents or preliminary reviews (Preliminary reviews deal with substances for which toxicological information s limited) have been initiated in 1973 or will be initiated in 1974 are given in Table I.

TABLE I

PRIORITIES FOR THE PREPARATION OF WHO CRITERIA DOCUMENTS AND PRELIMINARY REPORTS

	to be initiated in	
	1974	1975
Criteria documents	manganese	nickel
	nitrates, nitrites	vanadium
	nitrosamines	sulfates, H_2SO_4 aerosol
	PCBs	fluorides
	mycotoxins cadmium	chlorinated biocides and chlorine
	mercury	arsenic
	lead	beryllium
	oxides of nitrogen	chromium
	asbestos noise	SO_2 and suspended particulate matter
		carbon monoxide
		ozone and oxidants
		polycyclic hydrocarbons
		carbon disulfide
Preliminary reviews	Sb, Bi	Li
	Se, Mo, Te	Ba
	Ti, Ge, Sn	La, Al, Ga, Zn
	organic dusts	Fe, Ni, Co, Pd, Pt
	selected products of petroleum industry	inert dusts selected plastics and plasticizers

The principle which has been used in the preparation of the criteria documents and preliminary reviews is that of an integrated approach, i.e. the exposure of man through various pathways (air, water, food, home and working environment) is examined simultaneously to arrive at a total exposure. Whenever possible, guidelines will be given for primary protection standards, i.e., "an accepted maximum level for pollutants (or its indicator) in the target or some part thereof or an accepted maximum intake of a pollutant or nuisance into the target under specified circumstances"(7).

Based on these primary protection standards procedures will have to be developed for deriving 'working limits' i.e. "maximum acceptable levels of pollutants in specified media other than the target designed to ensure that under specified circumstances a primary protection standard is not exceeded"(7).

WHO has no intention of proposing international standards except in specific cases, such as those associated with food safety or the pollution of international waterways; in other cases WHO and other international organisations have the task to provide the best available scientific information and guidance for setting up exposure limits. Such guidance should include specific reference to the geographical, climatic, social, economic and technological considerations as well as other public health priorities which governments should take into account in the formulation of regulatory policies for environmental control and in setting up of national standards for the quality of the environment.

More than thirty WHO Member States are collaborating in this program and an agreement has been reached with the United Nations Environmental Programme, UNEP, to support these activities.

REFERENCES

1. The WHO Environmental Health Criteria Programme (unpublished document EP/73.1), Geneva (1973).

2. Handbook of Resolutions and Decisions of the World Health Assembly and the Executive Board, Volume I, 1948-1974, WHO, Geneva (1973; WHO Off. Rec. No. 209, Part I, Geneva (1973).

3. United Nations General Assembly, Report of the United Conference on the Human Environment held at Stockholm, 5-16 June 1972, United Nations document A/CONF. 48/14, 3 July 1972.

4. Environmental Health Criteria, Report by a WHO Scientific Group (unpublished document EP/73.2) Geneva (1973).

5. Assessment of the Carcinogenicity and Mutagenicity of Chemicals; Report of a WHO Scientific Group. Wld. Hlth. Tech Report. Ser. No. 546, Geneva (1974).

6. Health Aspects of Environmental Pollution Control; Planning and Implementation of National Programmes, Report of a WHO Expert Committee, Wld. Hlth. Techn. rep. ser. Geneva (1974).

7. United Nations General Assembly, Preparatory Committee for the United Nations Conference on the Human Environment, Report of the Preparatory Committee, United Nations document A/CONF. 48/DC/13, 30 September 1971.

DISCUSSION OF THE WRITTEN QUESTIONS

BARTH

What is the best way to make available the results of the world environmental research to environmental protection administrators in terms they can understand and use?

BARTH

I believe that the best way to make this kind of information available is through a process of "agreed-to criteria documents," very much like Dr. Vouk has just discussed. In my opinion, an appropriate international body is really the best kind of organizational entity to put together such documents. There should be representation from senior scientists from many different countries so as to have different points of view. Hopefully, the documents would adequately reflect an evaluation of the world's pertinent literature. Now, I would also hope that, as a result of this and other meetings and cooperative agreements, that world scientists and environmental health specialists can get closer together in terms of the way in which they design and carry out their experiments and the way in which they report their experimental data. The better the research, the more comparable the research and the better the quality assurance techniques, the better the available data will be for incorporation into criteria documents which can serve as source documents for administrators of environmental protection organizations.

TREMOLIERES

Pour que les administratifs ou les décideurs puissent comprendre véritablement le document scientifique, je crois qu'il faut qui'il y ait une sorte de culture de base commune et par conséquent les critères qu'on leur soumet, doivent etre creusés. Je prends un exemple: on a pris des critères pour les cyclamates dans la saccharine et on note ces critères;

il y a eu un effet cancèrigène à des concentrations extrement elevées, et par conséquent on les a interdit. Pour expliquer véritablement ce que signifiait ce critère il faut aller beaucoup plus profond. En prenant l'alcohol comme exemple l'information scientifique doit etre comprehensible et la recherche poussée suffisant pour qu'une dinstinction claire puissent être faite entre au processus normal d'oxidation de l'alcool et un processus qui est consideré à present comme nocif etant donné qu'il induit an cataboliseme nucleique. Tout soit etre compris par un ensemble de populations, il y un problème de culture général qui se pose, il faut sortir de notre hyperspécialisation pour que nous ne soyons plus dans une babel ou chacun ne peut comprendre le langage du voisin mai ou on a une culture qui puisse permettre de comprendre de secteur à secteur effectivement ce que veut dire un travail scientifique preécis.

If those who take and implement decisions are ready to understand scientific documents, we must be aware that there has to be a sort of common basic culture and accordingly the criteria proposed should be carefully explained. Criteria were established for cyclamates and saccharin. In the name of these criteria - very high concentrations were found to be carcinogenic - cyclamates were banned. To give a complete explanation of what this criteria meant, one would have had to go much more in depth. Taking alcohol as an example, the information must be made comprehensible and scientific research must be taken far enough for a clear distinction to be made between the normal process of alcohol oxidation, i.e. dehydrogenated alcohol, etc. and processes now considered to be harmful because they induce nucleic catabolism, etc. In other words I think there is a body of scientific knowledge which we cannot ignore and this raises a particular problem in our time. This must be understood by the masses and the question of general culture arises. We must end our overspecialization and emerge from a tower of babel where nobody understands his neighbour's language into a culture where from sector to sector the meaning of a specific scientific study can be comprehended.

BARTH

What forms of pollution are found in the developing countries and what environmental research, with what results have been conducted in developing countries, particularly Africa?

GOLDSMITH

I am going to introduce my remarks by further comment on the previous question. As an occasional reader and occasional contributor to criteria documents, I think that the communications need more than the written word. I think it needs personal communication and it needs especially, and the question is addressed to this, an appreciation of the fact that conditions in different places, different jurisdictions, are often very different and I especially want to emphasize that a standard or even a criterion which is highly significant and must be enforced and promulgated in a European country or a North American country or a South American country may be completely inappropriate to conditions in other developing areas as in Africa. So the first answer is that one must not try to copy environmental health regulations uncritically and the best protection is active interchange with people who know local conditions as well as the research. The specifics of the research in Africa which I know deal with the effect of housing variables on infant broncho-pneumonia mortality which has been done by Soffolui, on naso-pharyngio cancer by Dr. Winder and in New Guinea by Cleary which is also on housing and pollution. Then, of course, there are a great many problems of occupational health which developing countries may devote their resources to with considerable benefit and substantial protection. Since most of the occupations are associated with industries that may also produce community pollution, the opportunity to combine the effort is a very important one. Finally, in the communicable disease area, there is a very interesting study on cerebrospinal meningitis and its transmission through housing. I might just conclude by saying that by stressing the importance of domestic exposure to health in such research as has been done in Africa, the scientists have called attention to neglected areas in other parts of the world and I think we should recognize that this is a very substantial contribution of theirs.

BIERSTEKER

I think that basically the problems in the developing countries and in what we call the developed world don't differ too much, except that the accent in the developing countries is still on basic sanitation. Due to a lack of funds, and maybe also a lack of interest of the general public, the pressure for strict control on industries is less than we experience. As for the studies, I think the amount of money available to conduct studies in these countries is limited. I spent about six weeks in India in December of last year and January of this year and I think they are willing to do studies; they have planned to do studies, but so far, have had little financial assistance. On the other hand, I think if we look at it from a global point of view, some of the situations there may yield more information than we can find at home. I thought India had no smog problems but when I was in Delhi there was smog for more than a week, a very bad smog. The planes couldn't land. This was really very impressive. So our concepts about what's going on in other parts of the world are sometimes completely wrong. I think they are facing the same problems that we are trying to solve but there is just a time gap.

BENINSON

I think that if we go to the primary standards, the standards relating to tissues, concentration in human tissues, I would guess the results would come mainly from the more developed countries where a lot of research is being done. I think these values with some qualifications could be used as well and it would not be very wise to attempt to duplicate research with less possibilities. However, when those standards have to be translated into environmental standards, and to derive working limits, then the ecological chains are still important. To transfer parameters in these chains would be quite different one place from the other. Therefore, I think the emphasis in developing countries would be to study the transfer mechanisms in the characteristic environment of that place. For example, if studies are done for transfers through a deposition mechanism on the grass, passage through milk, and then human consumption, the results would have little value in a place where milk is not produced. Emphasis should be given to the particular food chain which would be characteristic and critical, (critical in the sense of transmitting a larger amount of a given pollutant). I think this would be a priority in developing countries.

VOUK

Since I come also from a developing country, I would like to make a brief remark. There is no clear distinction in the field of environmental health between developing and developed countries. Of course, as Dr. Biersteker stressed, the biological type of pollution resulting from lack of sanitation, is the major problem and will remain so for a long time in the world as a whole. But there are regions in highly developed countries, where lack of basic sanitation is still of major importance as recent outbreaks of some waterborne diseases have demonstrated. Similarly, as Dr. Biersteker stressed, there are some areas in developing countries where one can find heavy chemical pollution situations because of very rapid industrial development and urban development.

BARTH

What specific screening tests or other procedures would you recommend to delineate individuals or population groups who are especially vulnerable to certain environmental agents?

GOLDSMITH

Screening tests have not been tried extensively in environmental health although many of them should and could be. The most important general yardsticks are that people with inherited biochemical defects or chronic heart or lung diseases are exceptionally vulnerable among those on the disease category.

Special attention, I think, has got to be paid to the effects of pollution on children. We have had some very interesting contributions, both experimentally and epidemiologically, to the importance of early exposure to lead. I think that in the future, we have to increase the proportion of our attention that we pay to effects on children on growth and development.

BIERSTEKER
I can think of a number of ways of screening people on the basis of chemical tests. So, far, there has not been much use made of specific screening tests. The group which deserves special attention is the group of pregnant women. Upon further chemicalization of the environment, pregnant women, not themselves, but the unborn fetus may well act as a monitor to pick up other kinds of risks. A group which has been used for these studies is, of course, the group of patients with chronic bronchitis. On what basis they have bronchitis is not as relevant as their acting more or less as a barometer in the environment. Some of the most valuable work is being done in England and other areas. This has been possible thanks to the cooperation of these people who act as monitors in these studies.

BARTH
Why has so much time been spent at this Symposium on air pollution research and is it possible to apply data from studies alone for decisions on the protection of human health?

BARTH
To start with, we had to consider those papers which were submitted for this Symposium. Clearly, there is a great deal of interest in the various nations conducting environmental research in conducting research in air pollution. There just happened to be a predominantly larger number of air pollution research papers which were submitted to us for the Symposium. It was not feasible to go through and completely balance out

the papers that were in the area of air pollution control, water pollution control, noise, etc. If we were to maintain a strong scientific integrated approach to the program. The question, "Is it possible to apply data from such studies alone for the decisions on the protection of human health" -- certainly not. The information which one gets from air pollution studies will help insofar as air pollution is concerned. It has aspects not only with air pollution control for public health but also for occupational health. It certainly is applicable for occupational health and to public health, but when one is concerned with protection of the environment, one must be concerned with the total environment. It is never enough to look just at air pollution. One must look at the collection of air pollution, water pollution, soil pollution, food pollution and so forth -- the entire aggregate has to be looked at in order to develop adequate protection guides.

TREMOLIERES

Cette question est très pertinente car c'est finalement sur un plan métabolique que se juge une toxicité et laisser toute cette toxicologie dans des secteurs spécialisés c'est précisément s'écarter de cette espèce de background commun qui permet finalement de répondre aux divers secteurs spécialisés qui ne sont intéressés qu'aux applications.

This is a very pertinent question because toxicity is ultimately assessed on a metabolic level and to divide the whole of toxicology into specialized fields is to ignore this kind of common background which in the long run, benefits the various specialised sectors, which tend to concentrate on applications.

BENINSON

I will agree entirely that air pollution alone cannot be the basis for protection. In many cases, levels in air of a given pollutant may be quite low, but the deposition of that low concentration in air onto the ground and into a significant food chain may cause a substantial contamination of man and, therefore, the overall picture has to be studied for each

pollutant -- all the chains leading from the source to man.

BARTH

Would it not be desirable to encourage the use of data accumulated from the provision of health services in the conduction of environmental health research?

RECHT

Depuis un certain nombre d'années l'OMS a docifié les causes de décès; et classé les maladies; les nomenclatures existent et l'analyse des données épidémiologiques peuvent donc etre faites. Un point soulevé dans cette question de réferrait à la possibilité de comparer actuellement des données depuis 1960 à des données plus anciennes. Il est certain que ces difficultés existent, mais cela n'empeche pas que cette comparai peut donner des information sur l'évolution du phénomème; l'interprétation ne doit pas être faite en termes absolus. Il y a un second point qui était fort important il concernait le role du corps médical; le Panel y a été très attentif, l'information, l'éducation du corps médical est actuellement insuffisante pour lui permettre de collaborer aux études épidémiologiques nécessaires pour l'environnement. Or, comme nous l'avons vu, un très grand nombre d'études épidémiologiques sont basées sur des informations des examens médicaux et requiert, par conséquent la collaboration du médecin traitant et du médecin praticien. Dés lors un effort particulier d'information et d'éducation doit etre réalisé, spécialement dans le domaine de certaines enquetes qui toucheront des régions caractéristiques et concernant certains domaines que l'on n'a pas abordés ici mais qui sont très importants. Deux examples:

- l'ensemble des facteurs qui interviennent autour de naissance; il est impossible actuellement de conduire, selon des méthodes valables, parce qu'on ne l'a jamais fait et on ne c'est jamais mis d'accord sur une méthodologie, des enquêtes relatives à la périnatalogie. Or, la périnatalogie joue un role -

essentiel dans l'apparition des anomalies congénitales et l'environnement est certainement responsable pour une partie de ces anomalies;

- **Le second probléme a été la question de la bronchite; la bronchite chronique qui est considérée comme un élément important, 10% de décès au Royaume-Uni, 3 à 7% en France et des chiffres analogues dans plusieurs pays de la Communauté Européenne, est un probléme complexe et que sans la coopération du corps médical on ne peut pas arriver à répondre aux désiderata d'une méthode scientifique.**

For a number of years causes of death have been codified and a classification of diseases made by WHO; a nomenclature thus exists and epidemiological data can therefore be analysed. Reference was made to the possibility at this stage of comparing post 1960 data with older data. This problem does exist, we agree, but such a comparison can still give information on the trends without having to be interpreted in absolute terms. A second very important point concerned the role of the medical profession; the Panel has devoted much attention to this and it felt that the present state of information and training of the medical profession is inadequate for it to participate effectively in environmental epidemiological studies. As we have seen, very many epidemiological studies are based on information from medical examinations and thus require the collaboration of the specialist and the family doctor. A special information and training effort must thus be made, especially in connection with certain surveys concerning characteristic regions and certain fields which have not been mentioned here but which are nevertheless very important. I quote two. The first concerns all the factors which occur around the time of birth. At present it is not possible to conduct surveys by valid methods because this has never been done and there has never been any agreement on a methodology for perinatal studies. Yet, perinatal observations play an important part in the detection of congenital abnormalities, and the environment is certainly responsible for some of these. The second field concerns bronchitis. Chronic bronchitis is considered an important factor (it is responsible for 10% of deaths in the United Kingdom and 3-7% in France; the figures are similar for several Community countries). Bronchitis is certainly a complex problem and without the cooperation of the medical profession we cannot arrive at a scientifically sound answer.

BARTH

What is the importance of understanding biological mechanisms of environmental pollutants in recommending required control measures?

BUTLER

Control measures usually involve placing limits on the releases of environmental pollutants so that the amounts reaching the most sensitive receptor are below those causing unacceptable risks of harm. Thus one must know whether the effects of interest are short-term and caused by a concentration exceeding some critical value for a brief period, or whether they are long-term and caused by the prolonged accumulation of the pollutant or its effects in the receptor. The limits to be imposed will be quite different for the two modes of action.

BARTH

In estimating environmental hazards how important is an understanding of environmental transformations which the pollutants undergo?

VOUK

Man's exposure to environmental agents is either direct, such as by contact with chemical or exposure to certain physical hazards, or indirect, involving pathways through one or several environmental media (air, water, soil and food). In most situation there will be various, and often complex, pathways by which pollutants may reach man. Experience has shown that certain exposure pathways are much more important than others; these pathways are called "critical." Identification of critical pathways is of great practical value because it will usually indicate which population groups are likely to receive higher exposure than others, depending on their habits, occupation or age, etc., ("critical population groups"). The knowledge of critical pathways and critical population groups will simplif and reduce the cost of monitoring and will make effective control measures possible.

Often a series of chemical transformations occur before a pollutant reaches its human target. In many cases these chemical or biochemical transformations produce substances which are more toxic than the original pollutant. A well-known example of a complicated pathway through the food chain is that of methyl mercury, but others may also exist, for instance, tin, platinum, gold and thallium can be methylated in the environment, but the methyl group cannot be transferred in biological systems to lead, cadmium or zinc. Similarly, biochemical transformations involving methylation are expected for arsenic, selenium and tellurium. These biosynthetic processes are influenced by pH, temperature, and by the presence of other chemical species; for instance, the biological methylation of metals is inhibited by some chlorinated hydrocarbons.

Complex chemical and photochemical transformations of pollutants can occur also in air. Some of these have been extensively investigated as, for instance, the formation of the photochemical complex. Much less is known about the atmospheric transformation of sulfur dioxide and the relationships of nitric oxide to nitrogen dioxide.

BARTH
What is the importance of developing standardized data services to make rapidly available results of environmental research, and what quality assurance procedures would be necessary?

VOUK
A major problem today facing both scientists and regulatory agencies is how to bring relevant scientific and technical information from the published literature and miscellaneous sources to those who need it. In dealing with pollutants, it is essential to know their chemical structure; secondary product formation; pattern of usage; production data paths of disposal or environmental "sinks"; animal and human

toxicology; synergistic effects with other pollutants. There are already several centres and data banks where attempts are being made to store such information. Most of these data banks are specialized and cover only a part of the information which scientists or decision-makers in the field of environmental health may wish to have. Some of them are computerized search systems, such as TOXLINE or MEDLINE. The Toxicological Information Response Centre (TIRC), which has been established in the USA at the Oak Ridge National Laboratory in 1971 and which is sponsored by the National Library of Medicine (NLM), aims at building up a toxicological data base, to collect and disseminate toxicity information in the form of bibliographies, reviews and state-of-the-art reports, and to answer specific research requests from the scientific community. Another example is the Environmental Mutagen Information Centre (EMIC) which has been collecting data on the mutagenic action of chemicals since 1969 to the present and made this information available in a number of publications. Most of the existing systems, however, are designed in different ways and for specific kinds of uses, and it is therefore difficult to build up from them a general data bank and information centre to serve different types of users. An integration of such systems is undoubtedly needed, but a rigid framework is unlikely to provide the most serviceable system. A flexible approach, as conceived by the International Referral System for Sources of Environmental Information (IRS) of the United Nations Environment Programme, would have the best chance of being useful and acceptable. Maximum flexibility should be incorporated in planning such a system, so that changes in uses and needs may be taken into account, if necessary, for data storage and presentation.

Of course, most of these systems have little or no quality assurance procedures incorporated, and it is difficult to see how that can be done without a detailed evaluation of the original information contained in scientific articles.

This evaluation can only be done by experts in a particular field, and would give the best results if done on an international basis. The WHO environmental health criteria programme (a short description was presented in my opening statement) is an example of a system which aims at providing balanced and unbiased, internationally acceptable, information on the relationship of exposure to environmental pollutants and hazards and effects on man's health. One obstacle to the use of available information is that it has, in most cases, been obtained by different methods, both for measuring exposure and for assessing biological response, and that the results obtained in different laboratories, in various countries, are sometimes not comparable at all. A prerequisite for quality assurance of information on environmental levels of pollutants and their effects is the harmonization of methods for monitoring pollutants, for toxicological testing, and for epidemiological studies. Several international organizations, including WHO, are making efforts in that direction.

BARTH

How does one determine the levels of uncertainty of knowledge that will be acceptable to an Environmental Protection Administrator for his decision?

BIERSTEKER

There is only one way to find this out and that is in actual practice. If the pressure from politicians and (or) the public opinion is strong enough, environmental protection is possible in the form of source control or emission reduction without too much information on adverse health effects. A fixed level of uncertainty (or certainty) to take action without public pressure is hard to establish, I fear, as this may be a matter of character and temperament of the administrator. In general, administrators have learned that it is impossible to wait for complete certainty and that action without it is justified. This is nothing new in public health administration.

BARTH

It is possible to reach agreement on the definition of "risk" criteria for various environmental pollutants?

BENINSON

I believe risk criteria will be the trend. Standards based on risk are of normal use at present in radiation protection and the same approach can be used for other pollutants, particularly taking into account the stochastic effects for which no threshold can be readily demonstrated. The panel's introductory statements should be examined closely.

BARTH

How important are annoyance reactions and irritation effects in setting protection guides?

BIERSTEKER

They are in my opinion very important, for the public in a welfare society is less and less willing to accept nuisances. The reason is probably that the public feels that with a bit more care and some extra engineering efforts, such effects on the environment are avoidable. Consultation with sociologists and psychologists who are able to measure public feelings and establish tolerance levels should be part of the standard setting process. A difficulty is that in the course of time the tolerance and attitudes of people are apt to shift.

BARTH

Is there a practical way to integrate qualitative dose-response information with quantitative information?

BENINSON

Qualitative response-dose information can be used in setting standards by assignment of some quantitative character. For example, by rank ordering procedures or selection of suitable sample groups of people for frequency assessments in the case of annoyance or irritation effects. Even the absence of observations may give upper limits of the slope of a non-threshold relationship, in the given confidence levels.

BARTH

How is it possible to consider and judge the relevance of several subcritical effects occurring at the same time?

BENINSON

When several effects of a given pollutant can occur, it is possible to give a quantitative indicator of the total by the use of the concept "detriment" as presented in my introductory remarks. It requires the establishment of severity weighting factors for each effect. If several pollutants, each with a standard based on risk, act at the same time, safety could be assessed by the relation $\Sigma\frac{C_i}{S_i} < 1$, where C_i is the level of pollutant i and S_i is its standard.

BARTH

Once an apparent threshold value has been determined for an effect in relation to an exposure as measured by conventional means, to what extent, if at all, should more sophisticated measurement procedures be sought to attempt to find effects at lower exposure levels?

GOLDSMITH

The demonstration and acceptance of evidence concerning one threshold for a pollutant is no reason to think that for another population or another effect other data are not relevant to control needs. These effects need not even be at a lower level of exposure. In my view, threshold concepts should not be applied to human population reactions. I prefer to look at a set of criteria, which research continually refines.

BARTH

This concludes the written questions from the participants as summarized by the panel. The panel now stands to receive questions from the floor.

DISCUSSIONS FROM THE FLOOR

NEEDLEMAN (U.S.A.)

How can we achieve a scientific data base upon which to make health decisions, if we are not provided with a complete, unbiased presentation of the data? For example this morning we heard a report of neuropsychological performance in children in Smeltertown USA. The report found no deficit in children with blood lead levels greater than 40 µg/100 ml. some of us have had the opportunity to read the Center for Disease Control Bulletin of May 1, 1974, which showed precisely the opposite, studying the same sample. What are the causes for such discrepancy, and why were they not aired in the presentation of the paper?

GOLDSMITH

This may be aside from the assignment of the panel, but in a free scientific society, all types of communication by people of scientific stature, of course, are welcome. Some of them, of course, will not agree with others and, in this case, I think the disagreement is apparent. I want to refer back to my opening remarks in which if you are going to use information for establishing policy decisions, then the peer review process of publication confirmation and having authoritative scientists accept the fact that the document is relevant is a very important part of the process. I think that this is one of the ways to make sure that scientific controversy is recognized and resolved in the most suitable way. We cannot, however, have a free exchange of scientific information without the hazard that papers will give conflicting information some of which will be either biased or will be suspected of bias. Only the insistence on open availability of research results, on peer review and validation, and on calibration and confirmation of the data base, can assure that scientific results will be dependable. Concerning the particular session, no doubt the lack of time not lack of desire or intent was responsible for the superficial discussion of the paper in question.

BUTLER

I would just like to add a word to this. Mr. Chairman, this example just reinforces what you and Dr. Vouk have said about what is required for establishing a solid scientific base of criteria for environmental standards. That is that you need a committee of experts, preferably international, where all points of view and all conflicting bits of information can be brought together and the differences resolved. In my view, this is the best answer that one can give to the question.

HINE (U.S.A.)

At this time I wish to comment on matters pertinent to the Plenary Discussion Group's deliberations. I consider it mandatory to maintain a system of checks and balances so that we can arrive most precisely at acceptable community levels of pollutants. Those who work in the gathering of data should have a limited role in the critical evaluation of their own conclusions. They should have a still lesser role in the setting of standards. Criteria documents should not ignore significant negative data nor should they cite positive findings if they are not confirmed by others or are of questionable relevance. The experimental base should not be located solely in government laboratories.

There should be an effective mechanism for review of all data used for establishing air quality criteria. Not only should the opinions of qualified scientists in industry and academia be solicited, but their opinions should be carefully considered, evaluated and where appropriate, included. Past experience leads to the inescapable conclusion that these comments, though sometimes solicited, are almost always ignored. Finally I raise the question of the propriety of any group to function in all three activities of data gathering, standard setting and enforcing these standards.

RECHT

Je suis un peu étonné de ce type de réflexion car tout ce que nous avons appris au cours de ce Symposium a permis de constater que l'investigation épidémiologique était une science difficile à laquelle ne pouvaient pas participer des amateurs; à partir du moment où sur le plan scientifique, sur lequel nous sommes, on applique des méthodes qui sont bien connues en statistique et en épidémiologie, tout ce qu'on a dit se révèle être soit de la politique ou de la polémique mais pas de la science. Or nous savons que, sauf peut-être aux Etats-Unis ou en Grande-Bretagne et dans quelques secteurs isolés des pays européens, nous sommes sous-développés en ce qui concerne les études épidémiologiques et ce sera une constatation vraisemblablement de ce Symposium. Nous le sommes et nous devons suivre les exemples qui nous sont donnés, qui ont ête donnés par ceux qui ont participé aux réunions mais je suis tout-à-fait d'accord avec l'orateur précédent que la question du contrôle est un problème qui est très important, mais ce contrôle n'est pas un problème scientifique. A partir du moment où vous avez une équipe qui est constituée, elle doit pouvoir répondre aux lignes d'une recherche scientifique bien établie.

I am rather surprised at this attitude because everything we have learned during this Symposium has pointed to the fact that epidemiological investigation is a difficult science unsuitable for amateurs. As long as proven methods in statistics and epidemiology are applied at the scientific level, everything just said turns out to be either politics or polemics and not science. Yet we know that with the possible exceptions of the United States or Britain and some isolated examples in Europe we are underdeveloped in the field of epidemiological studies and this will probably be one of the conclusions of our Symposium. We are underdeveloped and must follow the examples given during this Symposium. I quite agree with the last speaker that the problem of surveillance is very important and that this is not a scientific problem. From the moment a team is established it should be able to follow the lines of well-defined scientific research.

MOLLARET (France)

Le richissime catalogue de documents recueillis par le symposium ne doit-il pas conduire à proclamer les déductions pra-

tiques à imposer d'urgence à l'attention des autorités gouvernementales internationales et avant tout sur la sauvegarde du capital en eau potable?

Should not the wide selection of documents gathered by the Symposium be used as a basis in order to choose the practical measures which national and international bodies should be asked to take.as a matter of urgency? One example of an item requiring immediate safety measures is our most valuable and most threatened asset, drinking water.

BARTH

The papers presented at this Symposium will most certainly be used in the development of criteria, standards or means of choosing practical measures of abatement of pollution. As I understand there are plans in the European Communities to have one or more colloquia regarding drinking water pollution. In the United States, our Congress will be preparing legislation to enable the Environmental Protection Agency to develop regulations and conduct research on drinking water supplies.

KJELLSTRÖM (Sweden)

I think the panel has presented some interesting views. I would however like to take up three points.

First, we had this morning some small discussion about the carcinogenics and the priorities - which ones we should study, etc. I think it is very important that we as scientists say what the priority should be on whether new possibly carcinogenic compounds should be introduced at all in the environment. If we can stop them before they are out in the environment, so much the better. It is the ideology of negative proof as we sometimes call it in Sweden, that has been accepted by the National Food Administration; e.g., they had in principle forbidden all synthetic colors to food.

Second, I think the documentation of any TLV values or any standards that we set must set forth the basis for the reasoning behind such standards otherwise people in other countries cannot make their own evaluation. I think the Czechoslovakians and the Americans have been broadminded when they published the documentation of their industrial TLVs, whereas it is extremely hard to get the Soviet Union documentation. In Sweden there is no documentation at all, but I hope that some will be available very soon because the TLV list has been redone. So I would say that it is necessary that we have a TLV or a standard for the environment which is completely medical; that the criteria for this medical decision be defined exactly; and that the documentation be published so that any country can determine if the documentation supports the TLV or the standard. Then if some country wants an administrative TLV which is higher or lower, it is up to them.

I understand that the developing countries have problems with their environment and these problems did not have a very high priority in the panel discussions. I would say that there is a great need for some kind of future research where concerned scientists who know the methodology in environmental research sit down and think out what can happen in these developing countries when industries are introduced. I think that this could prevent a lot of disease caused by pollution of the environment. Also let me say that methyl mercury incidents should show us that there is a great need for us as scientists to push for banning of dangerous substances, which are not really so necessary to us. We have banned methyl mercury in Sweden. Why have we not banned it everywhere so that they won't get a new kind of poisoning say in Central Africa?

BARTH

I would like to first comment myself on our being taken to task for the amount of time devoted to a single subject. Without question we could discuss any of the questions that have been asked for the entire two hours. We had to make a decision about the amount of material we wanted to cover in the panel discussion. We concluded that it did not make much sense to limit our discussions to one single question. Now on the other questions that you are raising, I believe Dr. Beninson would like to make a remark.

BENINSON

I don't think you can directly ban anything which is considered carcinogenic in the sense that you may do away with some of the benefits from the use of these materials. In every case I think it is a cost/benefit analysis. Take a very old and known example; if it were known at the beginning that X-rays would be carcinogenic, as we know at present, they would have been banned at the time. It is possible that we have cases of induced leukemia from X-rays, but quite surely many more people would have died from TB and other diseases. In the medical sense as a whole, there has been a marked benefit over the risk. I feel that in every case a cost/benefit analysis should be done. Banning for the sake of banning of a potential carcinogenic agent may be doing something of a disservice if the benefits outweigh the risks or potential health impact.

MOKEMATKEMGUEMBA (République Centrafricaine)

Nous attirons l'attention des hommes de sciences car les recherches dans le domaine de l'environnement doivent être objectives et universelles d'autant plus les maladies causées par les effets de l'environnement peuvent être transmissibles, donc il ne faut pas seulement limiter les recherches sur l'environnement dans les pays développés.

Il faut également aider les chercheurs des pays en voie de développement afin que les efforts dans le domaine de l'environnement soient conjugués.

We seek to attract scientists because research on the environment must be objective and universal; especially diseases caused by the effects of the environment can be transmitted, research must not be confined to the environment in advanced countries.

Researchers in developing countries must be assisted so that *efforts in this field can be coordinated.*

GOLDSMITH

Perhaps this meeting has not emphasized enough the problems of developing countries. Possibly the pollution and environmental health problems of developing countries deserve a meeting which could stress such problems as the tendency to "export" pollution problems from advanced countries, the unique opportunities for mutually worthwhile research in developing countries, and the wax in which the potential conflict between development and environmental quality can be transformed into strategies for effective efforts to encourage both. In this way researchers of both developing and developed countries can approach their respective problems together.

LAFONTAINE (Belgique)

Je voudrais ramener le débat à la sérénité nécessaire et arriver à ce que nous voyions chaque chose selon son importance et son urgence. Je souhaiterais aussi que l'on distingue les accidents des risques liés à un usage normal comme je demanderais qu'on n'oublie pas que pour agir contre la pollution de l'environnement il faut disposer de ressources naturelles et ce problème est plus à considérer encore lorsqu'il s'agit de pays en voie de développement.

Je souhaite poser trois questions

- d'abord lorsque des mesures ont été mises en oeuvre, comment se rendre compte de leur efficacité à l'égard de la santé et n'est-il pas important de prévoir à cet effet des études épidémiologiques prospectives ou le généraliste doit, si possible, jouer un rôle;

- par ailleurs, les approches sanitaires ont trop souvent suivi les aspects sectoriels des milieux d'où vient l'agression. N'a-t-on pas trop oublié que l'homme est l'intégrateur des nuisances et n'est-il pas utile d'avoir des approches multisectorielles, sauf dans le cas où le point d'impact est unique (effet irritant de la pollution de l'air sur les poumons par exemple)?

- Enfin, en plus des effets directs sur la santé, il ne faut pas oublier les effets indirects provenant des répercussions écologiques comme par exemple la pollution thermique évoquée ou l'atteinte à certaines productions alimentaires.

We must consider each issue in terms of its significance and urgency. I would also like a distinction to be made between accidents and risks inherent in normal use and I hope also that it will not be forgotten that natural resources are required to control pollution of the environment; this problem is especially acute in developing countries.

I would like to ask three questions:
- *Firstly, after measures have been applied, how are we to assess their efficiency for health protection? Shouldn't provision be made for prospective epidemiological studies in which the general practitioner could also participate?*

- *Secondly, the health protection approach has too often been a sector-by-sector consideration of pollution sources. Ought we not to remember more that man is an integrator of pollution and that it is sensible to adopt an overall approach, except when there is a single point of impact (e.g. the irritant effect of air pollution on the lungs)?*

- *Thirdly, as well as the direct effects upon health, we must remember the indirect effects arising from ecological repercussions e.g. thermal pollution or effects on certain food chains.*

BIERSTEKER

We should agree fully with Dr. Lafontaine that if the authorities plan to take action, they should follow up whether there is any measurable improvement in populations. The situation in London, which improved so much with the reduced smoke concentration, was used for this type of follow-up and there are similar situations in many parts of the world. I think that all engineering efforts to improve the environment should have a medical effort as well. There is also more need to stress the ecological effects. Basically we see that the medical profession is manipulated into a corner when concerned with the environment. The experience in Holland is that the environment is now handled by almost anybody except by the medical profession. The Royal Society of Medicine in Holland doesn't have a position on environmental problems. The doctors, in general, are not really interested. It is really hard to get many students interested in the environment except for a very short, superficial overview.

The vacancies which exist for the medical profession cannot usually be filled because of lack of interest. I think unless the medical profession is well aware that they should and could play a role in the environment, the health responsibility will slip out of their hands. The solutions to the problems in the environment will be found by the public itself and by other professions.

TREMOLIERES
Votre deuxième question me paraît tout à fait centrale et résume beaucoup de malentendus des questions d'aujourd'hui. Vous avez insisté sur l'épidémiologie. Mais je pense que si derrière l'épidémiologie il n'y a pas une bonne clinique, que si derrière l'épidémiologie il n'y a pas une bonne clinique, que si derrière la bonne clinique il n'y a pas une bonne toxicologie, que si derrière la toxicologie il n'y a pas une étude de la métabolisation très profondément vue, on ne se comprend. Je m'excuse, on parlait tout à l'heure de la compréhension au sein d'organismes internationaux et je me permettrai de faire une confidence: je fais partie depuis 1949 des Comités "calories", puis "protéines" FAO-OMS. Il faut d'abord se comprendre entre experts; on a dit sur les avitaminoses tellement de bêtises; je le dis très directement étant donné qu'on a envoyé à des prisonniers des choses qui ne servaient à rien, qui a vu des amitaminoses pendant la guerre, elles ont été rarisimes. Alors la compréhension entre les savants demande une formation des savants eux-mêmes, c.à.d. une déspécialisation qui permit à

spécialisé de comprendre ce que veut dire le secteur voisin. Il nous faut bâtir à l'heure actuelle une nouvelle hétérodoxe, et même tres hérétique. On parlait des publications tout à l'heure; publier quelque chose qui est une approche globale présente les plus grandes difficultés. Il faut avoir une conception globale de cette métabolisation des substances étrangères dans laquelle il y a tous les secteurs qui sont représentés ici.

I think that your second question, concerning an overall approach, is fundamental and explains many of the misunderstandings in today's questions. You emphasize epidemiology but I think that epidemiology must be backed up by good clinical knowledge, which must be seconded by good toxicology, which in turn must be supported by a very thorough study of metabolization. Otherwise communication breaks down concerning the metabolic aspect of health protection and debates like these result.

A moment ago we were discussing comprehension within international organizations. I may say that since 1949 I have been a member of the FAO-WHO Committees on Calories and Proteins. First of all the experts must understand each other; so much rubbish has been said about avitaminoses, such useless things were sent to prisoners: who ever encountered avitaminosis during the war? It was very rare. Comprehension among scientists requires training of the scientists themselves; i.e., despecialization to permit each specialist to understand the language of the next.

What we need today is a new approach, a heterodox and very heretical approach. Publications were mentioned a moment ago. It is very difficult to get something which adopts an overall approach published. What we need is an overall conception of this metabolization of foreign substances covering all sectors represented here.

GOLDSMITH

Professor Lafontaine brought up a very important subject when he emphasises the need for epidemiologists to be involved in monitoring in what happens under a variety of circumstances. This is especially important when new technical procedures are being introduced about which the consequences are not fully known. Unfortunately there are many proposals by epidemiologists that this be done and very few times does the person concerned with the introduction respond adequately. Just now the issue is catalytic control devices and we see a very great difficulty in getting a recognition that the kind of background data and epidemiological monitoring that are indicated are being undertaken. With respect to the physician often getting boxed in a corner, I would like to draw a modest analogy. I have heard in the corridors, at least, a great deal of discussion about environmentalists. You may or may not like them, or you may or may not feel that what they are saying should be responded to directly. But I would like to insist that at least as a social phenomenon the influence of environmentalists is an important symptom, a symptom that the scientific and technical components of society are being insufficiently sensitive to problems that are disturbing a great many people outside of the sceintific and technical communities. The analogy I want to draw is that a physician in practice who is a good medical scientist, as well as a good medical practitioner, has a dual obligation. When a patient comes to him, as many in the community go to their health and environmental authorities with these problems -- some of them not very clearly stated -- his first responsibility is to respond to the symptoms, to make sure what the complaint is, to listen carefully, to analyse and to treat symptomatically; his second responsibility is to carry out a sufficiently good diagnostic survey so that the underlying features which cause the particular patient (in some cases the community) to have maladies is grasped in a reasonably effective way. I think that this relationship of the scientific and medical authorities to the community problems which are brought to them is often either too symptomatic or too scientific, but both I believe are necessary.

RECHT

The assessment of the efficiency of abatement methods on improving the public health is of paramount importance. We are hampered at present by the lack of sufficiently accurate data and sometimes even by the total lack of data regarding the health condition of the population at least with respect to those symptoms which may be influenced by environmental pollutants. By sensitizing the general practitioner to these problems and with his active collaboration much knowledge can be gained.

Man is the integrator of all pollutions, but we do not know yet how to evaluate the overall impact. This is one area where much effort should be placed and where the development lead loss.

DE ZEEUW (Netherlands)
I am very impressed with the amount of data which has become available at this meeting, but I wonder whether the question how priorities should be decided upon with respect to the collection of scientific data is not a question which should be asked. Decisions are based on several different inputs, scientific considerations, public pressure, etc. Ideally they should be based on the requirements needed to set protection standards, namely quantitative relationships between exposure and effects (or probability of effects). Scientists should polarize their research, giving priority to these quantitative relationships; an additional responsibility of scientists is to advise decision makers on the real needs for data underlying any standard. Who decides upon priorities necessary for obtaining the scientific data base required for decisions to protect human health, and how? What is the responsibility of the scientist for these decisions? Why hasn't the panel introduced this important problem of the responsibility of the scientist in priority-decisions?

VOUK
The problem of priorities in science is a very complex question, and I don't think that we can answer it this evening. It depends very much on the interest of the scientist, on the sources of finance, who does the research, for what purpose and so on. It is quite true that there is also fashion research. I have had the chance to visit a number of laboratories about a year or two ago where I saw such things going on. There were very few institutions which I visited which tried to look ahead

and plan their research accordingly. As regards the choice of priorities for studies, it's a very difficult question. Some time ago WHO Scientific groups met in Geneva and certain criteria were agreed on priorities for research and evaluation of existing information on health effects of environmental hazards. These were listed in my introductory remarks. But certainly, there is some need for looking ahead for preventive action rather than for corrective action, and if the scientists themselves are doing or concentrating on the topics which are only of current interest, I don't think that there is any prevention possible. A good example of a preventive view was really the development of atomic energy research. When the first atomic reactor was put in operation in December 1942, there had been already, a fairly advanced program in biomedical research under way.

BUTLER

I would like to defend the panel against this accusation that they don't think about research policy and give any idea about priorities. Many of us earn a good fraction of our salary by doing this. But it's not easy. If you don't mind, I will tell you some of my own experiences in my own country where in my division we are concerned with criteria documents for environmental pollutants. One of the most difficult questions we have is which substances are we going to study and produce documents on. The sort of thing that happens is that on one committee you can find a man who is highly respected, who has a very strong personality who speaks loudly and longly at great length in all meetings and most certainly his pet project is going to end up one of the first ones studied. This is one phenomenon. Another one, and I have wrestled with this problem not only in Canada but in some international organizations, is to design some sort of what we thought was a scientific way of evaluating the urgency of problems so that we could attack them in a proper order. We designed a system which we thought was perfect and as objective as possible. We put it through all kinds of committees and processes and finally it came to a meeting something like this where there were emotions and where there were people who had votes and who changed the whole priority order. Politics does enter strongly into the priority rating; perhaps this is just a fact of life. The problems that are worrying the most people in the country are, I suppose, the ones you have to attack first even though on some subjective scientific rating they don't seem to present much of a hazard.

BENINSON
If I may comment on the question that I think is an exceedingly important one. The answer of course would be that the research for this purpose should be polarized. On what lines? There are three main requirements: one in the biological line, it would be to assess more relationships between exposure and effect or the probability of the effect -- the quantitative relations -- and to be able to do so at low levels in tissues. Probably the research would start with higher levels and be able to extrapolate to lower levels. But the main aim should be to obtain results linking quantitatively exposure and effect for a given pollutant. On the ecological line, it should be to obtain values for transfer coefficients between compartments in the environment, so one would be able to predict what would be the effect of a given input in one compartment, what would be the resulting levels in other compartments and what would the exposure of humans be. In this respect I think there is perhaps too much effort on monitoring without having a clearly defined objective of the monitoring. The third line of research is more a technological type. It would be improvement of procedures to reduce discharge of waste products on one line and secondly to assess the feasibility of alternative procedures to be able to do the cost/benefit analysis, taking into account these alternative procedures. These would be the lines. Now which of the pollutants should be studied first? I think what we have seen in the Symposium so far shows that the selection of pollutants for research has been quite reasonable.

GOLDSMITH

I think if we have been led into a trap as a panel, it deals with the meaning of the word 'required' in the title of the panel. I think we are -- assuming that we are the ones who are capable of making what is required--making requirements for the scientific data base. In fact I think reality would indicate that it is a social and a political process which decides what the data base is that is required and we are only counsellors in that process and not those who set the requirements.

TREMOLIERES

Just one word to say that my priority is this metabolic aspect of toxicology which means that we can understand what we are doing, and that we can understand each other.

BIERSTEKER

I would like to make a last comment, I think that what so far has escaped medical attention is mainly the nuisance problem or the negative side of the beauty of life. I think if you listen to what the public wants and what the politicians begin to translate into action, this is really where the field of action should be. As you see the number of publications in this, there are a few doctors in Sweden and one or two maybe in the United States and that's all the interest there is for this subject. So, I think if we want to talk about fields which need exploration and medical attention I think this is a new field which should be explored.

BARTH (Conclusion)

I am sorry but we are going to have to terminate the discussion here, so I declare this session closed.

QUESTIONS SUBMITTED IN WRITING BY THE PARTICIPANTS AT THE SYMPOSIUM

EDITORIAL NOTE: These questions were submitted in writing by the participants to supplement questions posed to the panel by the Chairman (see Chairman's note). The panel took the prerogative of condensing and paraphrasing the participants' questions in order to fully cover the subject areas assigned for discussion in the limited time.

GOOTJES (Netherlands)
What is the best way to make the hesitating results of many expensive scientific projects in lots of countries (for instance the time pattern of concentration of a pollutant in the organs of man) more concentrated and integrated so that the administrator can use them better to convince the people about the justice of his -in the eyes of the people -- income consuming protection directives?

MOKEMATKENGUEMBA (République Centrafricaine)
On dit souvent que le problème de la pollution est l'affaire des pays industriellement développés, je voudrais savoir si des recherches pour déterminer le taux de la pollution ou pour déceler les effets de la pollution sur la santé de l'homme ont été déjà faites dans les pays en voie de développement en général et en Afrique en particulier? Quels ont été les résultats de ces recherches dans le domaine de l'Environnement? Sous quelles formes se manifeste la pollution dans les pays en voie de développement?

It is often said that pollution is a matter for the industrial countries concerned. What I would like to know is: whether any research has been carried out in developing countries and particularly in Africa to determine the level of pollution or to detect the effects of pollution on human health? What was the result of such environmental research? What forms does pollution take in developing countries?

OMENN (U.S.A.)
What specific population groups or specific screening tests would you recommend to delineate individuals or groups who are especially vulnerable to certain environmental agents?

Allow me to mention a few possibilities drawn from "eco-genetics" studies of inherited individual differences.

- inducibility of aryl hydrocarbon hydroxylase by polycyclic hydrocarbons: the induced enzyme converts the agent to the active epoxide carcinogen; 47% of population are minimally induced, 9% maximally induced. According to Shaw, almost all of 50 patients with lung cancer were high or moderate inducers. Presumably, hydrocarbons in the general air, as well as in cigarette smoke, induce these enzymes. High inducers in the population should be at greatly enhanced risk.
- anti-trypsin deficiency/partial deficiency and enhanced risk of early obstructive pulmonary disease -- from smoking and probably from other inhaled agents.
- glucose-6-phosphate dehydrogenase ($^{G}6$ PD) deficiency and risk of hemolysis from oxidizing agents -- anti-malarial drugs, sulfa drugs, methroquinone in moth balls; likely also the nitrogen oxides in the air.

Recognition of potential high risk groups in design of epidemiological investigations is important; otherwise, no statistically significant risk may be found in studies of overall population samples.

SULAIMAN (Nigeria)
In the discussions so far, more time has been devoted to air pollution than to other forms of pollution. Is it because this is a major problem in developed countries, or is it because this is a field where adequate research has been made, or is it because of the ease with which the parameters can be measured? Finally I would like to ask therefore whether it is possible to apply basic scientific data derived from this field alone for decisions on the protection of human health in general?

DENNIS (Canada)

Several speakers during this Symposium have stressed the need for scientific information for the purpose of political decision making and implied criticism of the scientist for the fact that cause/effect information is incomplete. A health effect implies an impairment of function; if health services are available people go to physicians to reverse or alleviate their impaired function; physicians record the functional impairment. The harnessing of this information would allow an ongoing evaluation of health effects in total populations and allow the identification of problem areas and a description of the populations within those areas. The use of this data source requires a commitment from which the political decision maker cannot be excluded. Would it be appropriate for this forum to come forward with a resolution to this effect?

NEWHOUSE (Canada)

Could the panel consider the question of mechanisms of the biological effects of pollutants especially air pollutants since this may make an important contribution to determining control measure. Little is known about this as yet but it should, at least, be identified as a problem which needs to be tackled. Understanding mechanisms might result in more specific (and thus perhaps more specific and cheaper contra-measures) recommendations to industry, etc.

OLOFFS (Canada)

Recent scientific progress, especially in the life sciences, has made older data highly questionable -- however valid they were at the time. In his paper, The Environment and the Protection of Human Health, Dr. Burger based his arguments largely on the comparison of leading causes of death in 1900 versus 1960: How valid is it to compare diagnosis made in 1900 with those made in 1960? For example, what percentage of what was called pneumonia and tuberculosis in 1900, may have consisted of cases of malignant neoplasms of the lung. Or, what are "1900 - gastritis" and 1900 - chronic nephritis" Versus "1960 - Carcinomas" or "1960 - Cirrhosis"?

BRAMAN (U.S.A.)
How do you plan to make any progress in developing (evaluations) information on those hazards which undergo environmental transformations? For example, almost no information (except that developed by myself) is available on arsenic transformations or on the chemical forms of mercury in the environment.

SCHNEIDER (Netherlands)
What is the importance of the "availability" of the scientific data base required? Is there a need for calibration possibilities of the parameters that determine the relationships between human health and environmental conditions? Should the users of the data base be able to refer to uniform harmonized or standardized data services?

STEELE (USA)
How does one go about determining the level or levels of uncertainty (that is lack of knowledge) that will be acceptable to the administration or politician in setting policy or in making decisions? Presumably, economic (resource) trade-offs and time effects are both at work here

SHERWOOD (U.K.)
The health of most communities is related more to economic factors than fundamental knowledge of environmental factors. International progress toward common pollution standards will therefore probably await common economic standards in all countries. Does the panel consider that agreement might be reached on "risk" criteria? The advantage of the risk criterion is that it takes account of varying threshold for groups of varying susceptibility. The disadvantage is the demand for more information from exposure situations, both occupational and environmental.

LINDVALL (Sweden)
Referring to Dr. Biersteker's paper, my first question is: How important are annoyance reactions and irritation effects in setting protection guides? Annoyance reactions may in them-

selves cover a broad field from annoyance to environmental factors, over subjectively perceived hazards of,e.g., toxic agents, to annoyance to completely imaginary risks. Also annoyance could be looked upon not only as an expression of discomfort but also as a precursor of disease or an indicator of increased stress load. What is the view of the panel on the practical way to integrate qualitative dose-response information and quantitative information? In other words, how should we evaluate the joint effect of magnitude and frequency? How should we be able to consider and judge the relevance of several subcritical effects at the same time? Interactions between such effects may take place in the biological, psychological, and social domaine as well.

QUESTIONS SUBMITTED IN WRITING BY THE PARTICIPANTS AT THE SYMPOSIUM AFTER CLOSING THE DISCUSSION

EDITORIAL NOTE: These questions were submitted following the discussion at the request of the Chairman to accommodate the participants who were unable to ask questions from the floor during the limited discussion period. The Chairman agreed to have the answers included in the proceedings.

WASSERMAN (Israel)

The definition of the term "exposure" refers to amount of a particular physical agent, it could be more valuable to consider the "time" parameter also.

BUTLER

I agree with your idea and the problem is simply one of the use of words. To those who wrote those definitions for the Stockholm Conference "exposure" meant the amount of harmful agent reaching the receptor, i.e., the critical organ. From this and a knowledge of the amount of the agent in the critical organ the dose could be calculated in terms of exposure X days per gram of tissue.

JACKSON (USA)

Would the panel comment in more detail on their view of the role of the scientist in decision-making and policy debate? In many of the questions and replies at this symposium there is an implicit assumption that the scientific community has both an obligation and an inherent right to establish research priorities and determine policy. This view of the appropriate role for the scientific community is, in my view, not only potentially counterproductive, but also clearly not based on the reality of modern society.

BUTLER

In my view the role of the scientist is to inform the public and the administrators as honestly and completely as possible about the facts. This may be a repetitive process consisting of questions and answers. The final decision, however, must be made by an administrator with due regard for politics and public views. The views of the public are particularly important since they control the votes and thereby the budget, and, after all, research and protective measures are undertaken to protect them and their environment.

DI FERRANTE (C.E.C.)

In presenting their results in meetings and journals should scientists try to explain the meaning of their research with regard to health and the environment and also clearly indicate the limits within which their conclusions ought to be used?

GOLDSMITH

It is a view that a scientist who, in describing his research, attempts to draw conclusions about a specific standard or criterion is at risk of distorting and hence impairing the value of his scientific work. On the contrary I strongly urge that scientists in meetings and journals should explain in the most lucid language possible the meanings of their research with regard to health and the environment but such communications should be separate from communications of research findings themselves.

GHETTI (Italia)
Si deve rilevare l'assenza di contributi riguardanti l'uso di "Indicatori Biologici" animali e vegetali per lo studio del deterioramento ambientale.

There is a noticeable lack of contributions regarding the use of animal and vegetable biological indicators for studying environmental insult.

BIERSTEKER
Dr. Ghetti raises a very important point, stressing the limitation of most of our present research in estimating long-term ecological repercussions on public health.

There is, fortunately, a growing concern with environmental pollution in, and outside, the medical profession, in fact almost more outside than inside, I would say. The primary role assigned to medical people by society,however, is to assess direct health effects in people in both qualitative and quantitative terms. This explains the fragmentary approach, which will probably persist for many years to come. There are possibilities to model the risk of environmental pollution on the basis of animal or plant studies. This is in fact the main cause of concern in many action groups. Whether man will be able to learn more from these models than from his direct medical risks, time will tell. The political impact of these action groups has certainly grown in the past decennia and this is a hopeful sign.

KUMPF (W.H.O. Copenhagen)
There are methods being developed designed to permit the premarket hazard evaluation of chemicals to forecast their possible health and environmental effects, based essentially on analogies with chemicals of similar structure and known health and environmental effects. Should consideration be given to derived or estimated environmental and health effects in

setting product and productive standards, i.e., would the panel consider such data a scientific data basis for decisions on measures to protect human health? However, as a long-term goal, does the panel consider it possible to arrive at positive lists of environmentally dangerous substances and specifically those which have a potential health hazard in the sense that such lists are used in food legislation?

BIERSTEKER

In the field of communicable disease control there is complete public information on the known causative organisms. There is no reason why we should not have, in a comparable way, lists of dangerous additives published regularly. However, this will probably not prevent people from using food with such additives; see the effect of labeling cigarettes as dangerous. Therefore a legal basis to exclude proven dangerous chemicals to appear in food over safe concentrations can and should be part of modern health legislation. International uniformity of such standards is highly desirable. New additives should not be admitted without screening for possible risks. This can be required from the producer demanding standard procedures. Estimated health effects can help in setting priorities in the laboratory programs that are necessary to screen additives. In connection with the large amount of work involved, international coordination of these activities is essential. As the environmental impact of chemicals also depends on their persistence in nature and their accumulation in food chains, testing for potential dangers in this case is still more complex than in food additives. The positive approach puts a heavy responsibility on the screening agencies, but as the only alternative is the trial and error method followed so far, there is little hope that the positive approach can be avoided. Compared with the cost of developing new chemicals, the cost of screening can not be prohibitive. The need for international coordination of this work again is evident.

BERLIN (C.E.C.)

In the case when deliberate reduction of one pollutant in a given environmental media is likely to lead to other pollution problems, how can the scientist provide advice for decision making regarding the relative cost/benefits in terms of environmental health of this situation?

BIERSTEKER

It seems highly improbable that there would be no ultimate possibility to control the secondary, usually unforeseen effect too. In the case of lead in petrol, for example, it is likely that a less harmful additive can be found. If a side effect of pollution control has to be accepted by a public health administrator, this can only be on a temporary basis as a necessary step towards complete improvement of the situation. Most side effects are unforeseen, however, and need correction instead of a trade off.

FREDERIKSON (UNESCO)

Would it be more appropriate from the start to carry out environmental health research and measurements in direct cooperation with the "polluters" (e.g. the industrial managers and engineers, etc.) to get a better understanding of and sound optimal solutions to the problems? Care must be taken that those who will suffer from decisions are heard and have possibility to take remedial actions. (I would like to warn about the use of the word "standards." It is polyvalent: for in meteorology "primary standards" is used in the meaning of the French word "etalion," refers to ISO and the International Association for Legal Meteorology).

BARTH

Carrying out environmental health research in direct cooperation with industries which may have to be controlled on the basis of data collected is not deemed to be a wise procedure. Even though both parties carry out the research fairly and honestly, there is always the appearance of a conflict of interest to all outside parties. A better procedure would be for the governmental agency to carry out its research independently, propose the indicated standard and then allow all affected industries and the public to comment on the appropriateness of the standard in a public forum prior to the standard's becoming effective.

STEENSBERG (Denmark)
Even if the panel is concentrating on the scientific data base I would be interested in having some more management oriented aspects covered: e.g., How should we try to define the role of the various professionals engaged in environmental protection work especially the administrator-experts? At present there is a risk that health aspects are not integrated in all stages of the decision process - sometimes because of administrative borders and a hesitancy to integrate medical and biological expertise in the new administrations. How could we on the administrative and laboratory (institute) side secure a closer cooperation between occupational health and environment health expertise? Again administrative divisions tend to oppose the necessary contact.

BARTH
In order to achieve the necessary interaction between administrators and scientists it is imperative that each appreciate the problems of the other. Once this knowledge base is attained the interaction occurs naturally since both scientists and administrators will realise that neither can do his job well without assistance from the other. It is clearly desirable that there be close coordination between occupational and environmental health. Perhaps the best way to assure this is to put both groups organizationally under the same government executive and then have that executive force the necessary coordination to the required degree.

STEELE (U.S.A.)

At the opening session the importance of methods of measurement giving reproducible and comparable results was mentioned. Three of the 155 Technical Committees of the International Organization for Standardization (ISO) are relevant to the subject of this Symposium. ISO/TC43 "acoustics", ISO/TC146 "Air Quality", and ISO/TC 147 "Water Quality". These committees are preparing ISO International Standards for methods of measurement. I should like to ask the members of the panel, if such international standards for methods of measurement will also be of use for collecting data required for making decisions and setting regulations in the protection of human health?

RECHT

l'application et la crédibilité de toute décision et de tout règlement dans ce domaine sont basées sur l'existence de méthodes analytiques sûres. La disponibilité de méthodes standards internationales pour la surveillance de l'environnement et la surveillance biologique est essentielle, afin que ces méthodes puissent être utilisées comme références lors de la calibration ou de l'harmonisation des méthodes couremment utilisées.

The enforcement and credibility of any decision or regulation in this area are based on reliable analytical methods. The availability of international standards methods for environmental and biological monitoring is essential so that they may be used as references when calibrating or harmonizing the methods which are normally in use.

ZAPHIROPOVLOS (Greece)

Assuming that the significance of epidemiological, clinical and toxicological studies mentioned is equal how could the harmonious and constructive collaboration among the referred disciplines be obtained. At national and International level? Should one substance be introduced into a community, what criteria and protection guides should prevail especially when opinions on the substance in question do not fully agree? I understand the significance of the uniformity in distribution and comparability when contracting out research work and other studies in determining exposure-effect relationships on which will be based protection guides, but still have some doubts on the methodology to be followed; i.e. should "absolutely comparable" or should a "certain freedom" prevail on large scale studies?

BARTH

Referring to the first question, present procedures for insuring harmonious and constructive collaboration, at the National and International level, in epidemiological, clinical and toxicological studies, are clearly less than adequate. Steps which could be taken at national levels which might be helpful would include: a) Placing all National governmental sponsored work in these areas under the control of a single National agency; b) if a) is not possible, develop interagency agreements among all involved National agencies to allow for joint planning of critical experiments in the three disciplines. Maximally effective international collaboration is not possible unless National collaboration is achieved first. International collaboration may then be brought about through institution of bi-lateral or multi-lateral agreements among collaborating nations to allow for joint planning of critical experiments.

Referring to the second question, when opinions on a substance to be introduced into a community differ, the establishment of criteria and protection guides may be extremely difficult. Important questions which must be answered in this regard are: a) have criteria and protection guides for this substance already been established in other communities, states or nations? b) If the answer to a) above is yes, how strong and convincing is the scientific basis for the established criteria and protection guid

In the event the answer to a) above is no, then one must consider the following factors. On what legal basis is it possible to set criteria and protection guides for the substances in question Whatever legal basis exists must be followed scrupulously. In many cases this will call for the holding of public hearings to allow the public to express its views. The responsible governmental agency must then weigh all the evidence it has at its disposal and render a decision for or against the establishment of criteria and protection guides for the substance in question.

Referring to the third question, in striving for uniformity and comparability in studies designed to determine exposure-effect relationships one must, of course, exercise rules of reason. It is not necessary, and probably not desirable, that all studies be "absolutely comparable". Such an approach could stifle innovative experimental designs. To the extent possible, however, I believe that all studies should be "relatively comparable" in the sense that it is possible to tie them together through some systematic procedure. For example, two different methods of measuring exposures to air pollutants would be acceptable if both methods were calibrated against a single reference method.

STUPFEL (France)

What has been learned through cooperation between air pollution monitoring networks, meteorological stations and epidemiological surveys? Are there experimental investigations in that field?

BARTH
Much has been learned through the cooperative use of air pollution monitoring networks, meteorological stations and epidemiological surveys. As an example a common method for selecting study and control groups for epidemiological studies involves proceeding from a determination of the important air pollution sources through a study of the local meteorology to a rough estimation of the different population exposures to be expected based on prediction transport models of one sort or another. All of these input data are of considerable value in designing an adequate air pollution exposure monitoring network for both study and control groups. Of course if there has been an adequate air pollution

monitoring network in place initially, some of the above considerations may not be necessary. In most cases, however, this has not been the case.

1965

EXPERIMENTELLE FORSCHUNG
EXPERIMENTAL INVESTIGATION
RECHERCHES EXPERIMENTALES
INDAGINE SPERIMENTALE
EXPERIMENTEEL ONDERZOEK

Vorsitzender - Chairman - Président - Presidente - Voorzitter

E.M. MRAK (U.S.A.)

THE STATE OF THE ART REGARDING THE EXPERIMENTAL INVESTIGATIONS OF THE EFFECTS OF POLLUTANTS

DAVID V. BATES

**Faculty of Medicine, The University of British Columbia,
Vancouver, Canada**

ABSTRACT *(prepared by the editorial board)*

In answering the question about "the state of the art" in (this field) one should begin by differentiating between the "state of the art" and the "state of science". The scientific knowledge consists in the thousands of experiments which have been conducted and on which our present understandings are based; the "state of the art" consists in putting this information together allowing for factors which are particularly difficult to measure, but yet which we feel instinctively should be taken into account, and in making the best judgment we can on the questions which many puzzled legislators in different countries constantly ask us.

While admitting that there are still gaps in our knowledge and much useful work remains to be done, we can be reasonably satisfied at the general state of the individual sciences (animal and human experimentation in controlled environments - epidemiological studies).

The state of the art of decision-making and of synthesis has still a long way to go and I believe it is our responsability as scientists to be participants in this process and give it every assistance.

Preceding page blank

INTRODUCTION

In his introduction to the conference on the health effects of air pollutants organized by the National Academy of Sciences in Washington in October 1973, Senator Muskie said "We must base environmental standards on the best evidence that the scientific community can develop, and we must not allow those standards to be compromised because they are difficult to achieve or because of costs. The scientific community, therefore, has a great responsibility. It is you who must show what levels of air quality are needed to protect the health of the people. It is you who must show how your experimental conclusions can be the basis for public policy decisions. You must show who is in danger from dirty air and what pollutants in what combinations and concentrations pose the danger. Public policy makers need this guidance in order to ensure that adequate protection is provided for all our people without creating costs and dislocations that are not justified by the needs of public health. As scientists, you are in the first line of defence for national environmental policy, and in air pollution you are the most significant line of defence. It is people, not plants or fish, whose health and welfare may be affected, either positively or adversely, by your findings, your doubts, and your questions."

During this conference many thousands of words will have been added to those already published on the evidence on which reasonable decisions can be made. My title, given to me by the organizers of the conference, is "The State of the Art". Perhaps we should begin by differentiating between the "state of the art" and "the state of the science". The scientific knowledge consists in the thousands of experiments which have been conducted on which our present understandings are based; the "state of the art" consists in putting this information together and in making the best judgment we can on the questions which Senator Muskie and many other puzzled legislators in different countries constantly ask us. I would like to begin, therefore, by making some comments on the state of the science and conclude by trying to summarize the state of the art.

CLASSES OF EVIDENCE

There are three main categories which are customarily used in the study of air pollution, and in determining 'acceptable' levels of human exposure:

1. Animal exposures to pollutants.
2. Human exposures to pollutants in a controlled environment.
3. Studies of the epidemiology of human disease.

In the process of listening to much discussion during the past 20 years on this issue, I have come to feel that one of our difficulties is that we are not sufficiently aware of the advantages and disadvantages of these different methods of study, and we do not analyze often enough the ways in which the information derived from them can be used. I think it is therefore useful to look at all three categories of evidence and observe the ways in which any particular experimental approach is strong, and the ways in which it is weak.

1. Animal Exposures

Animal exposure experiments have formed the basis of the definition of toxic levels of a wide variety of different substances. In the case of exposures to gases, they indicate approximate toxic levels, provide very valuable information on the target organs being affected by different pollutants, and give us an opportunity to study long-term effects. The latter experiments, particularly if conducted on primates, are very expensive but nevertheless do give some indication of long-term exposure effects on body tissues. Sometimes people speak as if this kind of evidence is the only class to which we should pay attention. But there are formidable difficulties of interpretation. Thus, in experiments in which monkeys, for example, are kept at low concentrations of sulphur dioxide, all other aspects of their environment are carefully controlled. But what if sulphur dioxide predisposed to respiratory virus infections? Does the fact that there is apparently no histological evidence of damage in monkeys after one year of exposure to a given level of SO_2 have anything much to do with whether such a level of SO_2 is or is not an important factor in determining a higher rate of chronic respiratory disease incidence?

Quite apart from different effects on species, the average human working environment is a very much more complicated one than can be replicated in the laboratory, and there will always be doubts as to how safely we can transpose evidence of this kind into the human environment. Such experiments are extremely valuable in pinpointing the target organ, in indicating such things as cellular changes in the lung following gas exposure, and even indicating the effects of low concentrations in general on longevity. They will therefore inevitably remain an extremely important part of all such work.

2. Exposures of Human Subjects

It is relatively easy to study the acute effects of air pollutants on pulmonary function. Although the terminology and methodology used to measure pulmonary function are baffling to anyone who does not work in this field, it is fair to say that we have now reached a point of development when we are confident that the use of our presently available technology allows us to say with confidence whether or not a given exposure to a pollutant has or has not had any effect on the function of the lung. Such studies have, of course, the great advantage that we are dealing with the kind of population with which we are most concerned, namely ourselves; but there are difficulties in interpretation of such work. Such studies tell us nothing about the pathological changes that follow such exposures, and we have to reconcile the physiological change measured, with the histological changes observed in animal experiments. The general concurrence of this data is not too bad, but the cause of a reversible effect on function may be far from evident. Such studies also confront the major difficulty that we cannot use them to study long-term effects, and we also may be hesitant to expose individuals with lung disease, in the controlled laboratory setting, to levels of pollutants which they might well encounter if they were to fly into Chicago or Los Angeles on certain selected days of the year.

3. Epidemiological Studies

It would seem natural to suppose that the careful study of the incidence of human disease would be the final arbiter of the decision making in respect of all air pollutants. Certainly the tremendous and distinguished body of work which has been done in this field over the last 20 years has put us in a very much better position to try and decide what levels of pollutants we ought to agree are probably harmless. However, these studies always confront difficulties, particularly since there are so many interacting factors. Our sophisticated epidemiologists can usually handle these, but we are still left with difficulties. For example, it is all too easy to obtain negative results in such studies because the tools were inappropriate. There is a hazard that we may be content to approach new problems of pollution armed only with the weapons that seemed useful in other circumstances. It seems clear that the photochemical smog of Southern California does not produce the chronic bronchitis in large airways which was certainly a feature of the heavy particulate high SO_2 coal-burning type of pollution. So to approach the population of Los Angeles with questionnaires of respiratory symptoms that have been useful in a different environment may be asking the wrong questions. If a very long-term effect of air pollutant exposure had to do with accelerating the changes in the lung that are associated with age, what hope would there be that an epidemiological study based on incidence of hospital admissions would reveal this to us? The use of the computer, or as some would say, the misuse of it, is revealing possible associations between such things as oxide of nitrogen levels and hypertensive heart disease. It is easy to dismiss such associations whenever we cannot explain the possible intervening pathophysiology, but we have to bear in mind that the association between cigarette smoking and lung cancer was established nearly twenty years ago, but we still cannot name the carcinogen with confidence. Nevertheless, studies of human environmental effects are crucial and will obviously remain exceedingly important for many years to come.

THE STATE OF THE SCIENCE

Looking back over 20 years we can be reasonably gratified with the state of the science as it now exists. Admitting that there are many gaps to be filled, particularly in studies of combined pollutant exposure, nevertheless, we have a considerable body of animal experimental information which has given us a very good idea of early histological changes, mechanisms of tolerance, and principal histological targets for a wide variety of pollutants. These experiments have even indicated the possibility of long-term effects which are more subtle and more difficult to attribute to a specific change in any given organ. Our knowledge in this field is vastly superior to what it was 20 years ago. Similarly, we have developed methods of measuring pulmonary function that are very sensitive, and we have a better idea today of the functional consequences, or absence of them, of exposures to low levels of sulphur dioxide, oxides of nitrogen, and ozone, than we had ten years ago. There is much more to be learned in this field and, as I shall be stressing in the paper I am presenting to this conference, we have to replicate conditions of light exercise in making these observations. There are hundreds of epidemiological studies and we have come a long way since the first of these was published. We do have reasonably accurate knowledge of the comparative effects of cigarettes and air pollution on the incidence of chronic respiratory disease, and we do have an idea of levels of SO_2 and particulate pollution which are likely to be associated with increased morbidity. Recently, the demonstration of respiratory disease in men working in New York tunnels exposed to high levels of oxides of nitrogen has put some kind of ceiling on human exposure levels for this pollutant for the first time. Admitting there are still many gaps in our knowledge and much useful work to be done, we can, I think, be reasonably satisfied at the general state of the individual sciences which make up this body of knowledge.

THE STATE OF THE ART

As I indicated when I began, the "art" is to put together the data from all these studies as a basis for decision making. When people begin to do this, we encounter a number of common confusions. Perhaps you will identify them from your own experience if I comment on them in detail. Firstly, there is the scientist who says that consideration of these broader questions is no part of his mandate. It seems clear to me, however, that scientists who have produced the data and know the constraints upon it better than anyone else, should take responsibility for trying to distil out the importance of the conclusions. Secondly, you will find those who say that the process of trying to make decisions on such disparate data as monkey exposure experiments and human field studies is a waste of time. It would be very much better, these people argue, if we reduced all air pollution to a graphical series of mathematical formulae and then established a firm threshold effect line. Such a mathematical approach would be very desirable, but breaks down when the requirement is to bring together evidence from three different fields in order to devise the best current opinion. Thirdly, one is confronted by the difficulty that some scientists do not recognize that science is, after all, "the best available hypothesis". There are some scientists who are so rigorous in their methods and methodology, and of course distinguished thereby, they do not recognize that most of science ultimately consists in devising a best available hypothesis and proceeding to attack it by new experimentation. The construction, therefore, of the best available hypothesis as to what levels of pollutant might be permitted in an urban environment if certain things are to be avoided, is in this sense a "scientific" endeavour. However, the decision as to what is "acceptable" or "unacceptable" in an urban environment is not a scientific matter, but a matter of opinion. I have listed in Table I some of the possible consequences of photochemical air pollution most of which have been observed. The question here is, "where do you put your personal line to indicate that an unacceptable condition has been reached?" Scientific experimentation has established these phenomena and given approximate concentrations for them, but where you say you are going to draw the line is a matter of opinion. I may say that it is my opinion that it is intolerable and unacceptable for a city to have an environment in which children cannot exercise without suffering a measurable impairment of pulmonary function. Having stated this opinion, I will have to be required to state whether this will be true on every one of 365 days each year, or whether I might permit such a circumstance for a few days. I will then arbitrarily draw some line in trying to define what I feel is an acceptable or an unacceptable state of affairs. In doing this, I will be influenced by my feeling that it is not safe to assume that there is no relationship between repeated insults to the lung affecting function, and the later development of irreversible changes of one kind or another. Since we do not have proof that this is so, others are free to argue that transient changes in pulmonary function can be ignored.

Wherein, then, lies the "art"? I think the answer to this question has to be that the art consists in making allowance for factors which are particularly difficult to measure, but yet which we feel instinctively we should take into account. How shall we protect people who may be particularly sensitive to certain pollutants? How can we be sure that we have taken account of combinations of pollutants, particularly gases and particles, which have not been exhaustively studied? How can we be sure that our safety factor has taken account of the fact that any system of air monitoring cannot be depended upon to detect the regions of highest concentrations? Can we make a statistical guess as to the highest concentration a person might be exposed to, if we know the measurements made by a given number of monitoring units over an area? Have we built in enough protection for the person who lives very close to an identifiable point source of oxides of nitrogen or of SO_2? Have we taken sufficient account of possible very long-term effects which existing human epidemiological studies could not have revealed? The art, it seems to me, is making a guess at these interrelated factors in order to provide the politicians with the guidance they need. The state of the art is constantly shifting, but is generally facilitated by virtue of the much larger numbers of people in all countries who are giving these questions serious attention. The understanding of the basis of this kind of decision making is not yet well advanced. In many countries the process of input to the politician is obscure or non-existent. In very few places has serious study yet been given as to how such dialogue may become effective in being one of the inputs into policy making. The refinement of this process is one of the greatest challenges which we confront today and one which we have hardly yet begun to solve.

I would conclude, therefore, that the state of the science is moderately healthy and certainly much stronger than 20 years ago, and still growing; but the state of the art of decision-making and of synthesis has still a long way to go and I believe it is our responsibility as scientists to be participants in this process and give it every assistance. Maimonides, writing in Cairo in the year 1193, gave some advice on the "preservation of youth", as follows:

> "Sunshine and Fresh Air
>
> The quality of urban air compared to the air in the deserts and forests is like thick and turbulent water compared to pure and light water. And this is because in the cities with their tall buildings and narrow roads, the pollution that comes from their

> residents, their wastes, cadavers, and offal from their cattle, and the stench of their adulterated food, makes their entire air malodorous, turbulent, reeking and thick and the winds become accordingly so, although no one is aware of it. And since there is no way out, because we grew up in cities and became used to them, we can at least choose a city with an open horizon, especially on the northeast and toward high mountains with limited forestation and outside water. And if you have no choice and you cannot move out of the city, try at least to live in a suburb situated to the northeast. Let the house be tall and the court wide enough to permit the northern wind and the sun to come through, because the sun thins out the pollution of the air and makes it light and pure."

With automobile exhaust, the effect of sunlight is not to purify the air, but to provide energy for a most complex series of chemical reactions, and thus we have a new problem which might modify Maimonides' advice. However, after 780 years, our problems are still urban problems, they still involve garbage disposal, and we still prefer to live in suburbs if possible.

1976

TABLE I

CONSEQUENCES OF AIR POLLUTION

WHAT IS ACCEPTABLE?

1. OCCASIONAL LOSS OF VISIBILITY SOME DAYS EACH YEAR.
2. 5% CROP LOSSES IN ADJACENT AREAS SOME YEARS.
3. INTERFERENCE WITH VISIBILITY ON MORE THAN 10% OF DAYS.
4. MAJOR CROP LOSSES OR ECOLOGICAL EFFECTS ON NATURAL VEGETATION.
5. IRRITANT EFFECTS ON EYES AND SORE THROATS A FEW DAYS EACH YEAR.
6. DEMONSTRABLE IMPAIRMENT OF PULMONARY FUNCTION IN SCHOOLCHILDREN AFTER OUTDOOR EXERCISE ON AT LEAST 30 DAYS EACH YEAR.
7. DEMONSTRABLE MORBIDITY IN SOME SECTIONS OF POPULATION ON HIGH POLLUTION DAYS ONLY.
8. DEMONSTRABLE EFFECTS ON PULMONARY FUNCTION IN CHILDREN AFTER OUTDOOR EXERCISE ON AT LEAST 90 DAYS EACH YEAR.
9. DEMONSTRABLE AGGRAVATION OF SYMPTOMS AND MORBIDITY IN SOME SECTIONS OF POPULATION ON CONTINUING BASIS.
10. DEMONSTRABLE ADVERSE MAJOR HEALTH EFFECTS ON POPULATION, i.e. INCREASED HOSPITALIZATION FOR RESPIRATORY DISEASE, INCREASED INCIDENCE OF LUNG CANCER, ETC.

LEGEND: These are listed as approximate possible consequences of increasing levels of photochemical or mixed air pollution. They are given in this order to focus attention on the question of where the line of "acceptability" should be drawn. Science provides the evidence for the presence or absence of these phenomena, but where the line should be drawn is a matter of opinion.

1977

THE EFFECTS OF LOW LEVELS OF SO_2 AND OZONE IN THE SAME ATMOSPHERE ON HUMAN PULMONARY FUNCTION

DAVID V. BATES[+] **AND MILAN HAZUCHA**[++]

+ Faculty of Medicine, The University of British Columbia, Vancouver, Canada

++ Department of Physiology, McGill University, Montreal, Canada

ABSTRACT

There have, so far, been few studies of the effects of common air pollutants on man studied under conditions of light exercise, and practically none in which the effects of combinations of pollutants have been investigated. We have studied the effect of 0.37 ppm of O_3 *and 0.37 ppm of* SO_2*, alone and together, on young normal subjects. In an exposure chamber, each subject undertook light exercise on a bicycle ergometer at a work rate sufficient to double his ventilation for a period of 15 minutes, followed by 15 minutes of rest.*

When breathed alone, 0.37 ppm of SO_2 *has no effect on the maximal mid-expiratory flow rate (MMFR) nor on any other measurement of lung function when breathed during intermittent exercise for two hours. When breathed alone, 0.37 ppm of ozone produces a just significant decline of ventilatory function at the end of a two-hour exposure. However, when these two gases are present together, in eight normal young subjects who were non-smokers, at the end of a two-hour period the MMFR had dropped to 67% of its initial value; the* $FEV_{1.0}$ *was 78% of its initial value; and the mid-expiratory flow rate (50% VC) was only 54% of the initial value. As in all previous studies, there was considerable individual variation. A two-hour exposure to 0.75 ppm of*

1978

SO_2 alone dropped the MMFR to 90% of its control value. We conclude that ozone and sulphur dioxide, when present together, are exceedingly irritative; that "standards" cannot be set for these pollutants unless the presence or absence of the other is specified; and that a combination of circumstances appears to be leading to the presence of these two pollutants together in a number of urban environments in what may well be hazardous concentrations.

1979

1. Introduction

During the past year, it has become increasingly evident that, in the future, we are likely to be confronted with new combinations of air pollutants. In some cities, such as London, the major reduction in particulate pollution and the increasing automobile density have led to levels of ozone of 0.15 ppm, as recently reported by Derwent and Stewart (1). This concentration presumably occurred in the presence of significant coexisting sulphur dioxide. In California, the classical photochemical air pollution, of which ozone is one end product, may be complicated by increasing levels of SO_2 as a consequence of the use of high sulphur fuel to meet problems of energy shortage. These two gases, in combination, are known to be more toxic to plants than either alone at equivalent concentration (2). The purpose of this communication is to report on the effects of ozone and sulphur dioxide, when present together, on pulmonary function of normal subjects under carefully controlled conditions.

2. Methods

The exposure chamber we have used has been described elsewhere (3). Ozone is generated from electrical discharge in oxygen, and SO_2 is added to the chamber from a tank. The sulphur dioxide is removed from the line to the Mast ozone meter by a scrubber of glass fibre paper impregnated with chromium trioxide in concentrated sulphuric acid. Ozone is removed from the line to the SO_2 meter (model 67, Scientific Industries, Springfield) by a scrubber of crystals of ferrous sulphate heptahydrate. The SO_2 is added to the inlet to the exposure chamber, and sampling of both gases is from a point about one foot away from the nose of the subject. As the exposure chamber is within a laboratory in an air conditioned building without external opening windows, the temperature and humidity vary very little from day to day, and the particulate load is negligible. The possibility of unwanted contamination from ambient air pollutants in the air of Montreal is remote.

All experiments have followed the same protocol. Observations are made at time zero, and the subject then exercises on a bicycle ergometer at a work rate sufficient to double his ventilation for fifteen-minute periods, alternating with fifteen-minute rest periods for the next two hours. Pulmonary function tests are performed at 30 minutes, one hour, one and a half, and two hours after the start of exposure. Our subjects have mostly been university students and, in the experiments of exposure to both ozone and sulphur dioxide, all have been non-smokers.

Forced expiratory flow volume curves were recorded by a Fleisch No. 3 pneumotachograph connected to a Hewlett-Packard (Model 270) differential pressure transducer. This was coupled to a carrier preamplifier and the resulting signal displayed on a storage oscilloscope equipped with dual trace amplifiers. This flow signal was simultaneously recorded on a four channel FM tape recorder for later playback and analysis. Four flow curves were recorded on each occasion, and the definitive value was taken as the mean of the two highest values of the four. The complete technical methodology and necessary precautions and calibration procedures have been fully described elsewhere (4). We have also been recording the "closing volume" and "closing capacity" during these experiments, using Xe^{133} as a tracer gas. The results of these experiments have been noted elsewhere (5).

Frank, McJilton, and Charlson (5) have computed the probable delivery rates of sulphur dioxide and ozone to different parts of the human airway. Exercise, by increasing flow velocity, and by virtue of increasing tidal volume and hence, the diameter of small airways, is likely to lead to a higher concentration of these gases deeper in the lung than would be the case under resting conditions. It has been a deficiency of many previous studies of exposure to air pollutants that observations have only been recorded on resting subjects, although the proportion of people who sit on the street compared to those who walk along it is low, and children are customarily very active out-of-doors - a point to which we will return.

3. Results

The physical characteristics of the subjects who have been studied with exposure to O_3 and SO_2 together are shown in Table I. None had any past history of significant chest illness, none had a family history of asthma or atopic illness, and all were non-smokers.

TABLE I

PHYSICAL CHARACTERISTICS OF NORMAL SUBJECTS
NON-SMOKING MALES

Initials	Age	Ht.(cm.)	Wt.(kg.)
WB	23	182	82
MG	21	182	80
FS	22	188	79
WW	20	185	72
JS	25	178	67
JR	21	178	82
LD	23	178	79
TE	19	188	84

In Table II are shown the results of the exposures to 0.37 ppm of SO_2 and 0.37 ppm of O_3, present together in the chamber, using measurements of maximal mid-expiratory flow rate. This test of function is the mean velocity of air flow during forced expiration of the middle half of a maximal expiration (i.e. between 25% and 75% of the recorded maximal expiration). As we have previously noted, this test together with the velocity at the 50% expiration point, are the two most sensitive indicators of change amongst those that we have studied (5).
It will be noticed that a significant fall in maximal mid-expiratory flow rate has occurred within 30 minutes of exposure. The table also shows the observations expressed as percentages of the initial value. We have recorded elsewhere (7) the variance of these ventilatory tests in normal subjects after exercise in our exposure chamber without any ozone or SO_2 being present.

As in all previous experiments of this kind, there is considerable variation in the magnitude of the effect observed. Thus, at the end of two hours of exposure, subject JS has an MMFR which is still 91% of the control value, whereas in TE it has fallen to only 35% of the initial

TABLE II

EXPOSURE TO 0.37 ppm O_3 AND 0.37 ppm SO_2
INTERMITTENT LIGHT EXERCISE

MAXIMAL MID-EXPIRATORY FLOW RATE
LITRES/SEC.

Subject	Control Time Zero	Hours of Exposure 0.5	1.0	1.5	2.0
WB	7.39	7.32	6.30	3.40	3.39
MG	4.37	3.96	4.24	4.18	3.90
FS	6.08	5.06	4.17	4.30	4.03
WW	6.03	5.16	4.47	3.60	3.78
JS	10.92	10.42	9.83	9.30	9.97
JR	8.62	7.27	7.38	6.40	5.75
LD	4.96	4.22	4.21	3.99	3.92
TE	9.91	7.15	5.13	4.64	3.47
MEAN	7.28	6.32	5.72	4.97	4.78
SD ±	2.36	2.15	2.03	1.98	2.22
SE	0.83	0.76	0.72	0.70	0.79
"t"	-	3.30	3.17	4.00	3.62
p (from initial value)	-	0.02	0.02	0.01	0.01

As Percentage of Control Value

Subject	Control Time Zero	0.5	1.0	1.5	2.0
WB	100	99.17	85.33	45.99	45.91
MG	"	90.81	97.13	95.79	89.36
FS	"	83.15	68.63	70.63	66.26
WW	"	85.47	74.17	59.61	62.59
JS	"	95.43	90.04	85.23	91.37
JR	"	84.29	85.65	74.23	66.71
LD	"	85.04	84.79	80.36	78.95
TE	"	72.15	51.82	46.83	35.04
MEAN		86.94	79.70	69.83	67.02

value. The mean fall in MMFR for the group of eight subjects at the end of two hours was to 67% of its initial value. The fall in forced vital capacity over the same period was to 82% of its initial value; of $FEV_{1.0}$, to 78% of the initial value; of peak expiratory flow rate, to 79%; of MEFR at 50% of vital capacity was to 54% of its initial value; and the static (non-forced) vital capacity was 92% of its initial value at the two-hour point for the group as a whole. Thus, the fall in the flow measurements was proportionately much greater than the fall in static volume.

In Table III are shown a comparison between the two-hour exposure values with ozone and SO_2, separately and together, by comparing the effect on a single test of pulmonary function, the MMFR.

TABLE III

CHANGES FROM INITIAL VALUE
AFTER 1 HOUR AND 2 HOURS OF EXPOSURE

INTERMITTENT EXERCISE - NON-SMOKERS

		PERCENTAGE OF INITIAL VALUE			
		Maximal Mid-Exp. Flow Rate 1/sec.		MEFR (50% of VC)	
GAS Composition	Number of Subjects	1 hour	2 hours	1 hour	2 hours
0.37 ppm SO_2	4	98	100	102	97
0.37 ppm O_3	3	96	88	98	86
0.75 ppm SO_2	4	91	89	82	76
0.75 ppm O_3	9	82	65	78	62
0.37 ppm O_3 and 0.37 ppm SO_2	8	80	67	71	54

It is to be noted that the subjects exposed to the two gases together, whose characteristics are shown in Table I, are different subjects from those from whom the other exposure data have been derived who took part in experiments we have reported previously (6, 7). It is apparent from this table that the effect of 0.37 ppm of O_3 and 0.37 ppm of SO_2 together is about comparable or slightly more severe than the effect of 0.75 ppm of O_3 alone. It is much greater than for each gas separately at a concentration of 0.37 ppm. This result is shown diagrammatically in Figure 1.

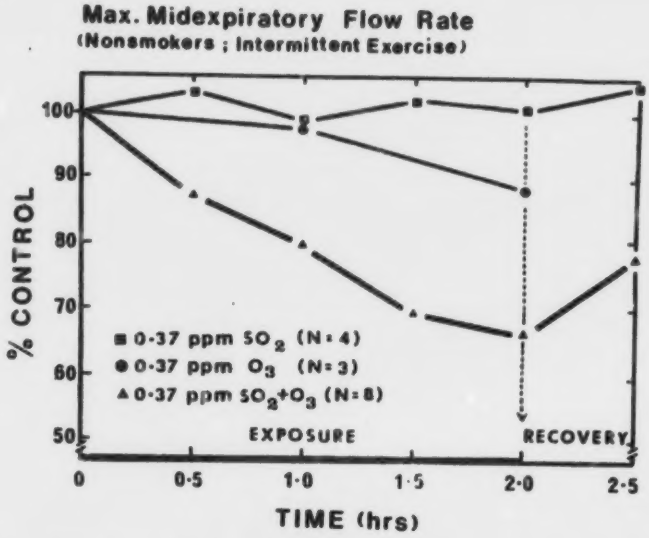


FIGURE 1 This figure shows the effect on maximal mid-expiratory flow rate of SO_2 and ozone, separately and together. Physical characteristics of the eight subjects exposed to 0.37 ppm of SO_2 and 0.37 ppm of ozone, existing together, are given in Table I. The fall in maximal mid-expiratory flow rate after two hours exposure to 0.37 ppm of ozone is just statistically significant (see Reference 7). The much greater effect of the two gases, when present together, is illustrated in this figure, the data from which is derived from Table II.

Since the exact mechanisms of these effects on the human respiratory tree are not fully understood, it is of interest and importance to study the rate of recovery after exposure to these gases as a guide to the kind of pathological process which may be occurring. The time course of function test change during two hours of exposure (with the same exercise protocol) and two hours of post-exposure recovery in non-smokers exposed to 0.75 ppm of O_3 is shown in Figure 2. The observation that none of these tests of function have returned to their initial control value two hours after the exposure has ended, requires emphasis. Some additional

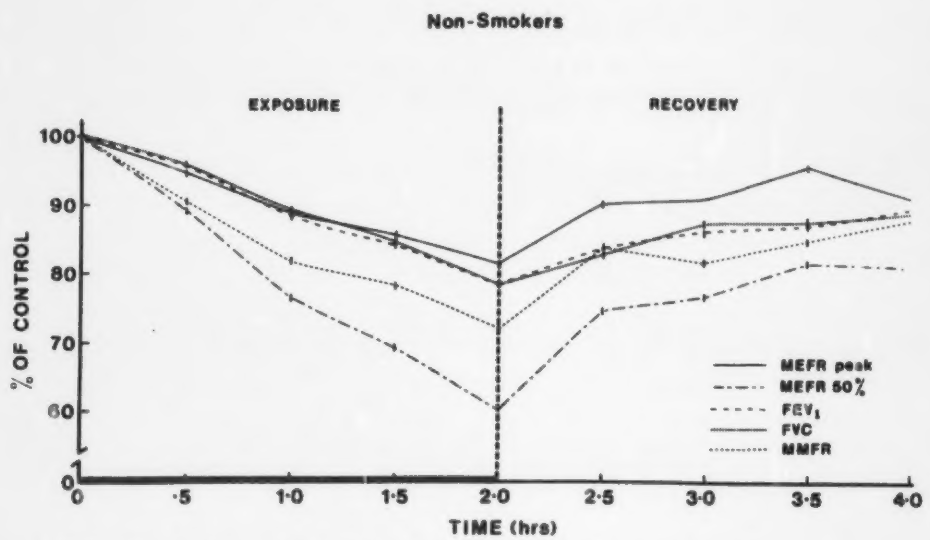


FIGURE 2 Figure 2 shows the time course of changes in five pulmonary function tests in a group of non-smoking normal subjects during a two-hour exposure to 0.75 ppm of ozone. Intermittent light exercise continued throughout the exposure period involving light bicycling for 15 minutes alternating with 15-minute rest periods. None of these tests of pulmonary function has returned completely to its control value within two hours of removal from the ozone, and a further period of between two and four hours was required for complete restitution.

experiments which we have carried out indicate that the control value is attained between four and six hours after a two-hour exposure period and all pulmonary function tests are back at their control values at that time (4).

We have noted constitutional symptoms, particularly chest pain, after exposure to 0.75 ppm of ozone and, on one occasion, one of the subjects had what might have been a small hemoptysis 12 hours after exposure. Clinical and radiological examination of him was negative, but a similar event has been recorded by others who have exposed normal subjects to levels of up to one part per million. In view of the cellular changes which occur in the lungs of animals exposed to levels of above 0.5 ppm of ozone, we would not recommend that the exposure of normal subjects to these concentrations under conditions of light exercise be lightly undertaken - indeed in our view the scientific purpose of such measurements would have to be very clearly specified for such exposures to be justifiable on an ethical basis. In our initial series of experiments at 0.75 ppm of ozone we used mainly physicians as subjects (6), and we have done no further experiments at this concentration.

4. Discussion

It is hardly surprising that these two highly reactive gases, which can coexist for relatively long periods of time at these low concentrations, should produce a greater effect on the human lung than either alone. The enhancement of toxicity of SO_2 and O_3, when simultaneously present, has been known to exist in plants for some years. As a first approximation, one can imagine the two gases, humidified in the airway and presented with a large surface area, rapidly combining to "paint" the smaller airways with sulphuric acid. This probably explains the relatively rapid effect which can be noted from the data in Table II. The MMFR had fallen to 87% of its control value within 30 minutes of exposure.

We find it hard to believe that all the effects are to be explained by edema of airways. The slow recovery after ozone exposure (see Figure 2) might be due to slow absorption of fluid, but in the absence of more specific understanding of the dynamics of fluid absorption under this circumstance, it is not easy to know whether resorption would require a four-hour period. A purely irritant reflex effect would have been expected to resolve even faster, however; the most that can be said is that the recovery time in excess of two hours should warn us that much more research is required (probably in animal experiments) on the mechanism of the effect of these gases.

Are these experiments reliable as indicators of what may be happening in the world outside the laboratory? The recent study by Lebowitz and his colleagues (8) has demonstrated a decline in $FEV_{1.0}$ in children and adolescents after outdoor exercise on days of relatively high pollution in Tucson, Arizona, as compared to days of relatively low pollution. From the data they present, it looks as if the maximal pollution to which these children might have been exposed would have been up to 0.28 ppm of ozone, 0.10 ppm of nitrogen dioxide, 70 microgram/cubic meter of particles, 4.0 microgram/cubic meter of sulphate, and perhaps 0.3 ppm of SO_2. It seems likely that it is the interaction of these pollutants that has caused the measurable effect, in line with the laboratory experiments we have reported here. Similarly, it seems likely to us that the high morbidity amongst children exercising out-of-doors in Japan, to which we have drawn attention (5), is to be explained by the simultaneous presence of O_3 and SO_2. These observations suggest that in many environments, measurable effects on pulmonary function might be observable if they were specifically looked for.

Are these experiments useful as indicators of "acceptable" and "unacceptable" environments? At the very least, they warn us of the dangers of setting acceptable levels of individual pollutants when combinations are likely to coexist. The question of whether we should accept as "acceptable" an environment in which one cannot exercise without a measurable decrement of pulmonary function occurring, is a matter of opinion. However, we cannot safely assume that long-term consequences can be dissociated from short-term repetitive insults of the kind that are probably now commonly occurring in a number of environments in different parts of the world.

It has been the purpose of this communication to bring this to your attention.

(Supported by grants from the Medical Research Council of Canada
and the Canadian Thoracic Society)

REFERENCES

1 DERWENT, R. G., and STEWART, H. N. M., Elevated Ozone Levels in the Air of Central London, NATURE, 241, 342, (1973).

2 MACDOWALL, F. D. H., and COLE, R. F. W., Threshold and Synergistic Damage to Tobacco by Ozone and Sulphur Dioxide, Atmosph. Env. 5, 553-559, (1971).

3 BATES, D. V., BELL, G., BURNHAM, C., HAZUCHA, M., MANTHA, J., PENGELLY, L. D., AND SILVERMAN, F., Problems in Studies of Human Exposure to Air Pollutants. Can. Med. Assoc. J. 103, 833-837, (1970).

4 HAZUCHA, M., Effects of Ozone and Sulphur Dioxide on Pulmonary Function in Man, Ph.D. Thesis (Physiology), McGill University, (1974).

5 Proceedings of the Conference on Health Effects of Air Pollutants, National Academy of Sciences, (November 1973), Serial No. 93-15, (U.S. Government Printing Office, Washington, D.C., Stock No. 5270 - 02105).

6 BATES, D. V., BELL, G. M., BURNHAM, C. D., HAZUCHA, M., MANTHA, J., PENGELLY, L. D., and SILVERMAN, F., Short Term Effects of Ozone on the Lung, J. Appl. Physiol. 32, 176-181, (1972).

7 HAZUCHA, M., SILVERMAN, F., PARENT, C., FIELD, S., and BATES, D. V., Pulmonary Function in Man after Short Term Exposure to Ozone, Arch. Environ. Health 27, 183-188, (1973).

8 LEBOWITZ, M. D., BENDHEIM, P., CRISTEA, G., MARKOVITZ, D., MISIASZEK, J., STANIEC, M., and VAN WYCK, D., The Effect of Air Pollution and Weather on Lung Function in Exercising Children and Adolescents, Amer. Rev. Resp. Dis. 109, 262-273, (1974).

DISCUSSION

BUTLER (Canada)

Is the enhanced response to the combination of SO_2 and O_3 due to an addition of two physiological responses or to the production of a more irritant chemical by reaction between the two gases?

BATES (Canada)

I believe that the most likely explanation is the formation of H_2SO_4 within the airways of the lung. The chemists whom I have consulted have pointed out that the drawing of the two gases into the lung would have three consequences favouring H_2SO_4 formation, namely humidification, heating and exposure to a considerable surface area. So I think the most likely hypothesis is that the airways are in effect "painted" with sulfuric acid.

I have no direct evidence that this is the case, however.

EFFECTS OF SULFUR DIOXIDE ON HEALTHY AND PERIPHERAL AIRWAY IMPAIRED SUBJECTS

FRANCIS W. WEIR[+] AND PHILIP A. BROMBERG[++]

[+] Research Laboratories, General Motors Corporation, Warren, Michigan, USA

[++] Ohio State University, Columbus, Ohio, USA

ABSTRACT

This report describes an investigation of healthy subjects and subjects with early signs of chronic obstructive lung disease exposed to atmospheres containing sulfur dioxide (SO_2). Experiments were conducted in a $28M^3$ dynamic flow environmental chamber maintained at 22 ± 1°C and 50 ± 5% relative humidity. Exposures to 0, 0.3, 1.0 or 3.0 ppm SO_2 were ordered in randomized sequences for 120-hour periods (Series 1-healthy men) or 96-hour periods (Series 2-unhealthy men).

In Series 1, no significant dose-related changes were observed in subjective complaints, clinical evaluations, or most pulmonary function measurements. Significant, but minimal, reversible decreases were noted in compliance at high breathing frequencies at the 3ppm exposure level, but these changes disappeared within 48 hours after cessation of exposures.

Clinical evaluations of Series 2 revealed a variety of subjective and objective findings. However, complaints could not be related to the concentration of SO_2. Inter- and intra-subject variability in the results from each pulmonary function test far exceeded the variance due to exposure to SO_2.

The evidence suggests that persons with minimal preexisting peripheral airway disease are probably not more susceptible to the effects of SO_2 *than normal persons. However, the existance of prior disease confounded any attempt to define threshold concentrations of* SO_2*.*

These studies have demonstrated that most conventional methods for assessing pulmonary function are insufficiently sensitive to detect early changes resulting from exposure to SO_2 *even in carefully selected healthy subjects and, further, that assessment of air pollution effects in the large portion of the population with pulmonary dysfunction may require development of entirely new methodology.*

(Research supported by the American Petroleum Institute).

1. Introduction

Recent legislative action, designed to control the levels of sulfur dioxide (SO_2) in the environment, has emphasized the need for more complete knowledge of the biological effects of this compound. Reports based on faulty or inappropriate observations have been widely employed as bases for legal standards. Adequate measurement of cause and effect has been a major problem. Retrospective epidemiological surveys of pollution have failed to demonstrate that environmental levels of SO_2 are causally related to deleterious health effects, since so many alternate, often confounding variables must be considered. Further, disease or death seldom, if ever, result from pollution alone.

Animal experiments have likewise yielded little appropriate information. The acute, reflex bronchoconstriction, studied in a variety of animals, is a convenient bioassay but is in no way useful in assessing the effects of chronic exposure (Nadel, et al.[1], Frank and Speizer [2], Amdur and Mead [3]). Regarding chronic effects, Alarie and co-workers [4,5] exposed guinea pigs and monkeys continuously for more than a year to levels of sulfur dioxide of about 0.1 and 1.0 ppm. These investigators found no changes in a variety of pulmonary and cardiac function measurements, blood chemistry studies, gas uptake, or histology of the respiratory tract which they could relate to the sulfur dioxide exposures. Evidently, the reflex changes observed in the acute experiments are not reflected as chronic effects.

Laboratory investigations employing healthy human subjects exposed to moderate concentrations of SO_2 (<5 ppm) indicate that the irritation effects are not debilitating and are rapidly reversible. Furthermore, when sequential exposures were performed, the reexposure to SO_2 was characterized by a much lower response than after initial administration (Frank [6], Frank, et al.[7]).

The present investigation was designed to quantify the concentration-time exposure levels of SO_2 in the atmosphere which does not produce subjective or objective deleterious effects in either healthy subjects (experimental Series 1) or subjects exhibiting early signs of chronic obstructive lung disease (experimental Series 2).

Experiments of Series 1 provide data useful for assessing the effects of SO_2 on healthy subjects. Subjects of Series 2 are representative of a large fraction of the population thought to be more susceptible than normal to the effects of SO_2, thereby making the results of the study more applicable to the general population.

2. Methods

2.1 Exposure Facility

The exposure chamber, a $28M^3$ room, utilized in this study was a design modified by Hinners, et al. [8]. The chamber was a truncated pyramid (3.5M/side) with straight side walls (1.8M high) supporting the pyramidal funnel structure. Sanitary facilities were installed in the chamber to allow prolonged occupancy.

Influent gas mixtures entered through a transition duct at the apex of the pyramid; effluent gas exhausted near the floor of each side wall.

Ventilation through the chamber was maintained at 0.5 changes per minute. All influent air was filtered to remove particulate matter. Temperature and humidity were controlled at 22 ± 1°C and 50 ± 5% relative humidity by an air refrigeration system and accessory electric heat supplemented with filtered live steam when necessary.

Access to the chamber was through a double door air lock system designed to allow researchers to enter the chamber without disturbing the gas composition.

The SO_2, anhydrous research grade, was metered into the influent duct down stream from the air conditioner. The flow rate of the SO_2 into the influent air stream was controlled by a capillary flow meter with a two-stage regulator system and needle valve.

Samples of chamber air were periodically collected in midget impingers and subsequently analyzed with the spectrophotometric technique of West and Gaeke, as modified by Scaringelli, Saltzman, and Frey [9].

Series 1 Subjects: Twelve healthy adult males between the ages of 21 and 28 were selected for the Series 1 study. In this series, all subjects were nonsmokers. Candidates were screened on the basis of motivation and extensive physical and psychological examinations.

Series 2 Subjects: Criteria for selection of subjects for the second series of experiments were based on the need for otherwise healthy persons exhibiting preclinical chronic peripheral airway obstruction. Males between age 25 and 49 years with normal chest X-rays, electrocardiograms, no history of asthma or significant allergy, no clinically apparent diseases, and satisfactory results on psychological examination, but

TABLE I

PLANNED EXPOSURE SEQUENCE FOR SERIES 1 AND 2 EXPERIMENTS

Subject Group	Exposure Week			
	1	2	3	4
I	1.0 ppm	0.0 ppm	3.0 ppm	0.3 ppm
II	0.3 ppm	1.0 ppm	0.0 ppm	3.0 ppm
III	3.0 ppm	0.3 ppm	1.0 ppm	0.0 ppm
IV	0.0 ppm	3.0 ppm	0.3 ppm	1.0 ppm

with evidence of small airway impairment were accepted. Airway impairment was defined on functional bases.

Subjects were accepted with abnormal Closing Volumes (CV), measured by methods described by McCarthy, et al.[10], depressed Maximum Mid-expiratory Flow Rates (MMF), and one-second Vital Capacity (VC) between 70% and 50% of total VC.

Only eight candidates from over 400 applicants qualified for the second series of experiments. Of these, one subject elected not to return after one week of exposure. The remaining seven completed the test cycle.

2.2 Exposure Protocol

The planned sequence of exposures to SO_2 for both series of experiments is presented in Table I.

During each 16-week series, all experiments were conducted using the double-blind technique. None of the operating personnel or the subjects were permitted access to the exposure sequence. The physicians responsible for daily physical examinations and overall subject health were also unaware of the exposure schedule until the end of the exposure series.

The design for Series 1 experiments was based on the assumption that four groups of three subjects would complete the series. Each group was exposed for 5 days (120 hours), followed by a rest period of nine days. For Series 2 experiments, each group consisted of two subjects, exposed continuously for four days (96 hours), followed by a rest period of ten days. This pattern was repeated for each of four exposure periods. A final evaluation of health status was completed within one week following the final exposure.

2.3 Pulmonary Function Tests

Daily pulmonary function measurements included Airway Resistance, Functional Residual Capacity, Static and Dynamic Lung Compliance, timed VC, Maximal Expiratory Flow-Volume Curves, CV, and Nitrogen Washout.

Airway resistance and functional residual capacity were measured by methods described by DuBois, et al.[11]. Static and Dynamic Lung Compliance measurement techniques were essentially those of Woolcock, et al.[12]. Vital Capacity and Flow-Volume measurements were determined with a dry-rolling seal spirometer coupled to an X-Y plotter. Closing volumes were determined by the spirometer and plotter coupled to a linear nitrogen gas analyzer. The method was essentially that described by McCarthy, et al.[10].

The nitrogen washout procedure was similar to the multiple-breath, open circuit technique described by Comroe, et al.[13].

2.4 Statistical Analyses

The experimental design of these exposures utilized a Latin Square for the selection change-over sequence but allowed for a sample size that is not rigid relative to a Latin Square. The order of administration of SO_2 was dictated by the use of a 4 x 4 Latin Square to determine the change-over sequence in each of the four weeks of treatment exposure. Treatment sequence was then allocated to four groups of subjects with three (Series 1) or two (Series 2) subjects in each of the four groups. It was recognized that this particular design is sensitive to a treatment carry-over effect, but it was further calculated that a 9 or 10-day resting period was appropriate based on past experience with healthy subjects.

Statistical analysis was performed by grouping the appropriate results to conform to a three factor randomized block design with each of the subjects acting as a separate block. Three factors considered were: subject, concentration, and week of study, with "N" levels of subject, four levels of concentration, and four levels of week (time). Each of the three main factors was tested for its level of significance by computing the appropriate F-value using the proper two factor interaction mean square as the error term. The analysis was repeated using a $\log_{10}$ transformation of the data where it was thought that subject response was not expected to be normally distributed based upon biological considerations.

Data reduction and analysis of all results from both series of exposures, were aided by use of an IBM 370/165 computer. All variables in these experiments were analyzed by the use of the Biomedical Computer Program BMD08V [14]. This program was designed to compute and analyze variance of two or more factors. Mean separation of significant data was accomplished with the Duncan New Multiple Range Test [15].

3. Results

3.1 General Observations (Series 1 and 2)

Daily examination of all subjects by a physician during both series revealed a variety of subjective and objective findings. Most of the presented complaints were randomly distributed throughout each series and could not be related to the concentration of SO_2 in the chamber. Furthermore, the number and degree of complaints or symptoms appeared to be randomly distributed throughout any exposure week, with the exception of the last day of exposure. Fewer complaints of ill health were reported during the last 24 hours of exposure than during any other period. The range of complaints included: headache, nasal congestion, sore throat, coughing, mild to moderate gastrointestinal disturbance, nose bleed, and skin rash.

On several occasions, a subject began an exposure week with a mild upper respiratory infection, including cough and sore throat. There is some suggestion, from the physicians' notes in the daily log, that recovery from the infection was slower if this situation occurred during the 3 ppm SO_2 week than if it occurred in any of the other test cycles. However, there were insufficient cases to verify this statistically.

No other dose-related patterns of complaints of symptoms could be extracted from the daily log or physicians' notes.

In most cases, subjects could not determine by sense the relative dose of SO_2 they were receiving during any week. Several subjects stated that they sensed something in the chamber atmosphere by taste during the 1 ppm exposures. These same subjects sometimes indicated that they were receiving the "highest" exposure during the 3 ppm week. All members of the investigation team were instructed to minimize thought and discussion regarding the probable concentration in order to maintain objectivity. Therefore, no consistent records were compiled regarding subject concentration-awareness.

3.2 Pulmonary Function Tests for Series 1

No dose-related changes were observed in most pulmonary function measurements of Series 1 subjects that could be attributed to SO_2 exposure. Significant, but minimal, reversible decreases were noted in the frequency dependence of compliance tests as a result of the 1 and 3 ppm exposures. The greatest decreases in compliances at high respiratory frequencies occurred after 24 hours exposure. Both 1.0 and 3.0 ppm exposure produced significant depression compared to controls at 24 and 48 hours after start of exposure. These effects became less pronounced as the exposures progressed through 72 hours. After 120 hours of exposure, however, the 3.0 ppm values were again significantly depressed. The daily pattern

TABLE II

SUMMARY OF PULMONARY COMPLIANCE

MEASURED AT 120 BREATHS/MINUTE FOR SERIES 1

Conc. ppm	Hours of Exposure					Week Average
	24	48	72	96	120	
0	0.200(a) (0.039)(b)	0.208 (0.037)	0.214 (0.041)	0.203 (0.049)	0.190 (0.037)	0.203 (0.041)
0.3	0.217 (0.052)	0.214 (0.055)	0.206 (0.056)	0.189 (0.041)	0.208 (0.044)	0.207 (0.049)
1.0	0.183(c) (0.047)	0.195(c) (0.039)	0.191 (0.036)	0.185 (0.054)	0.198 (0.049)	0.190(c) (0.045)
3.0	0.064(c) (0.051)	0.180(c) (0.037)	0.203 (0.037)	0.186 (0.054)	0.178(c) (0.042)	0.182(c) (0.044)

(a) Mean Value for 12 subjects expressed in 1/cm H_2O.

(b) Values in parentheses represent standard deviations.

(c) Significantly different from controls at $p < 0.05$.

of effects of exposure on the highest breathing frequency tested (120 breaths/min.) are summarized in Table II.

3.3 Pulmonary Function Tests for Series 2

None of the results from the pulmonary function tests illustrated clear evidence of differential SO_2 effect. In both the normal and $\log_{10}$ transformed data, inter- and intra-subject variability in the results from each test far exceeded the variance resulting from the exposure to SO_2.

There were scattered points within the test data which were significantly ($p < 0.05$) different from control; however, none of these represented a dose response of the subjects to SO_2.

The results of the frequency dependence of compliance test clearly demonstrated that Series 2 subjects had peripheral airway disease. In these subjects, even at the lower frequencies, the dynamic compliance was depressed compared to the static compliance. Healthy subjects (Series 1) performing the same test showed dynamic compliances at low breathing frequencies (20-30 breaths/min) not significantly different from results of the static compliance.

4. Discussion

These studies have shown that conventional methods of detecting lung obstruction, such as measurement of total airway resistance, are insensitive and fail to detect peripheral airway obstruction. The data presented indicate that there is a significant but reversible effect on the pulmonary function of healthy adult males by 3 ppm SO_2 exposures for 120 hours. The daily pattern of effect shown in Table II suggests that there are probably two mechanisms operating to produce the increased small airway resistance observed. Early after the start of exposure, both 3 ppm and 1 ppm SO_2 produced changes in compliance that are significantly different from control. These changes became less apparent as exposure proceeded. However, after 120 hours of exposure, the 3 ppm SO_2 data again became significantly different from control.

We reason that the early changes are the result of reflexive constriction of the airways, similar to those reported by Amdur and Mead [3]. These changes disappeared with continued SO_2 exposure. The later effects represent a breakdown in the adaptation processes at the 3 ppm exposure level.

We think the early changes observed as a result of 1 ppm SO_2 represent a threshold of effects for SO_2 in healthy subjects under the conditions tested. Continued exposure to 3 ppm SO_2 beyond 120 hours could possibly produce more persistant changes.

In regard to the Series 2 experiments, there is every reason to expect that pulmonary responses such as the frequency dependence of compliance response are only linear to the effects of SO_2 over a limited range. If the effects produced by SO_2 exposure are due to reflex constriction of the airways, then it is probable that persons with preexisting, nonreversible disease could not show further significant constriction in response to SO_2.

The evidence from the Series 2 experiments suggests that persons with preexisting peripheral airway disease are not significantly more susceptible to the effects of SO_2 than normal persons. However, the existance of prior disease confounds any attempt to quantify threshold changes from SO_2 that are minimal compared to the preexisting condition.

It should be noted that the changes reported in these experiments are minimal compared with the effects of smoking on frequency dependence of compliance. We reported as significant changes that were within 10% of control values. Smoking, on the other hand, depresses the compliance at high frequencies to as low as 40% of control values (Woolcock, et al. [12].

These studies have demonstrated that most conventional methods for assessing pulmonary function are insufficiently sensitive to detect early changes resulting from exposure to SO_2 even in carefully selected healthy subjects, and further, that assessment of air pollution effects in the large portion of the population with pulmonary dysfunction may require development of entirely new methodology.

REFERENCES

1 NADEL, J. A., SALEM, H., TAMLIN, B., Y. YOKIWA, "Mechanism of bronchoconstriction," Arch. Environ. Health, 10, 175 (1965).

2 FRANK, N. R., SPEIZER, F. E., "SO_2 effects on the respiratory system in dogs," Arch. Environ. Health, 11, 624 (1965).

3 AMDUR, M.E., MEAD, J., "Mechanics of respiration in unanesthetized guinea pigs," Am. J. Physiol., 192, 364 (1958).

4 ALARIE, Y., ULRICH, C.E., BUSEY, W. M., SWANN, H.E., MACFARLAND, H. N., "Long-term continuous exposure of guinea pigs to sulfur dioxide," Arch. Environ. Health, 21, 769 (1970).

5 ALARIE, Y., URICH, C.E., BUSEY, W.M., KRUMM, A.A., MACFARLAND, H.N., "Long-term continuous exposure to sulfur dioxide in cynomalogus monkeys," Arch. Environ. Health, 24, 115 (1972).

6 FRANK, N.R., "Studies on the effects of acute exposure to sulfur dioxide in human subject," Proc. Ray. Soc. Med., 57, 1029 (1964).

7 FRANK, N.R., AMDUR, M.O., WHITTENBERGER, J.L., "A comparison of the acute effects of SO_2 administered alone or in combination with NaCl particles on the respiratory mechanism of healthy adults," Int. J. Air and Water Pollution, 8, 125 (1964).

8 HINNERS, R.G., BURKART, J.K., PUNTE, C.L., "Animal inhalation exposure chambers," Arch. Environ. Health, 16, 194 (1968).

9 SCARINGELLI, F.P., SALTZMAN, B.E., FREY, S.A., "Spectrophotometric determination of atmospheric sulfur dioxide," Analytical Chemistry, 39, 1709 (1967).

10 MCCARTHY, D.S., SPENCER, R., GREENE, R., MILIC-EMILI, J., "Measurement of 'Closing Volume' as a simple and sensitive test for early detection of small airway disease," Am. J. Med., 52, 747 (1972).

11 DUBOIS, A.B., BOTELHO, S., BEDELL, G., COMROE, J., "A rapid method for measuring thoracic gas volume. A comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects," J. Clin. Invest., 35, 327 (1956).

12 WOOLCOCK, A.J., VINCENT, N.J., MACKLEM, P.T., "Frequency dependence of compliance as a test for obstruction in the small airways," J. Clin. Invest., 48, 1097 (1969).

13 COMROE, J.H., FORSTER, R.E., DUBOIS, A.B., BRISCOE, W.A., CARLSEN, E., The lung: Clinical and pulmonary function tests, Year Book Medical Publishers, Chicago (1962).

14 DIXON, W.J.(ed.), BMD Biomedical Computer Programs, University of California Press, Berkeley (1967).

15 DUNCAN, D.P., "Multiple range and multiple F tests," Biometrics, 11, 1 (1956).

DISCUSSION

BATES (Canada)

What was the level of physical activity during the exposure? Since most people walk in those atmospheres rather than sit at rest in them, it seems to me important that if such studies are to be used for standard setting, the protocol should include exercise. Using an exercise protocol, Dr. Hazucha at McGill has been able to demonstrate a change of closing capacity in normal subjects after two hours of exercise in 0.75 ppm of SO_2.

WEIR (U.S.A.)

1. During the described investigations there was no formal program of exercise. However, each subject was encouraged to continue his personal daily exercise including periods of a) running inplace, b) push-ups and c) deep-knee bends. These exercises were not quantitated.

2. Regarding Dr. Hazucha's studies, I agree that in normal, healthy individuals, it should be possible to show effects from short exposures to about 1 ppm SO_2. However, I contend that closing volume response to SO_2 or other contaminents is probably only linear over a narrow range.

Our data suggest that these responses will not be dose related when super-imposed on the pre-existing disease process in the more normal population, many of whom have early pre-clinical changes caused by other factors.

HAZUCHA (Canada)

I would like to ask Dr. Weir several short questions.

1. The interindividual variability of lung function tests is expected, however, I am surprised by your large intraindividual variability since some of the tests you used e.g. flow-volume curves are highly reproducible. Can you comment please?

2. Both dynamic compliance and closing volume measurement are presently considered to be the most sensitive tests for detection of the small airways impairment. However, while your dynamic compliance was altered significantly, the closing volume was not. Can you explain this discrepancy?

3. I certainly cannot agree with your conclusions that subjects with small airways impairment "are probably not more susceptible than normal population" (towards SO_2). Your data clearly show that they are more susceptible to SO_2, although you were not able to show statistical significance (yet?).

WEIR (U.S.A.)

1. Tests such as flow-volume curves are indeed highly reproducible in healthy individuals. There is a vast literature to support this. My contention remains that most of these "sensitive" indicators will not give reliable dose-response relationships when applied to the general population, many having preclinical small airways disease.

2. As indicated during my presentation, the closing volume test was not applied to the Series I, healthy subjects, but only to the Series II, unhealthy subjects. My comments to your first question apply here.

3. I am afraid that you misinterpreted my results. All quantifiable results indicated that the Series II subjects were not differentially sensitive to SO_2 compared to Series I subjects. Although the pulmonary function tests results were variable, the very careful clinical examinations conducted daily on these subjects as well as answers to subject inquiry of well being indicated no difference in susceptibility between these two groups of subjects in response to SO_2.

ZEILHUIS (Netherlands)

What should in your opinion be the consequences for the threshold limit value for occupational exposure. Your study suggests a "breakdown in the adaptation processes at the 3 ppm exposure levels" in highly selected healthy subjects, without more than minimal physical activity. Could you discuss the results of your study, trying to extrapolate these to occupational exposure, for say, 4 - 6 ppm SO_2, 40h/week + moderate physical exercise for workers with less healthy lungs than even your group II.

WEIR (U.S.A.)

Our results indicated that subjects representing at least some of the population generally considered to be "more sensitive" did not appear to respond to SO_2 to a greater degree than normal healthy individuals.

The 5 ppm SO_2 used for TLVs previously in the USA should adequately protect all workers likely to be exposed. Those individuals who are "sensitive" will not be further protected by decreasing the TLV to 2 ppm as has been suggested recently by NIOSH. Those persons would need an almost SO_2- free environment (essentially the environmental levels proposed by the EPA) to be adequately protected. I submit that those persons probably "self-select" themselves from exposure in our work environment.

GRUENSPAN (Federal Republic of Germany)

What effects do bronchodilators, antihistamines or atropine have on the lung function described?

Is the reduction in lung function due to the action of acetyl choline or histamine?

Are the phenomena observed attributable to bronchoconstriction caused by another factor?

WEIR (U.S.A.)

Unfortunately we had neither the opportunity nor permission from the University Human Research Committee to conduct what would essentially be pharmologic experimentation. It is probable that the observed effects could have been countered with drugs. I am of the opinion that at least some part of the response observed is reflexive and central nervous system controled.

The experiments your suggest should certainly be conducted to properly assess the importance of findings such as were presented in my paper.

BERLIN (C.E.C.)

Dr. Weir has just shown that exposure to SO_2 levels below 1 ppm do not lead to any apparent effects on pulmonary functions; it was further indicated that this may be due to the insufficient sensitivity of the conventional methods used.

In the previous presentation Dr. Bates had demonstrated that for SO_2 levels of 0.37 ppm combined with O_3 at the same concentrations lead to significant effects.

Both these conditions are not representative of the real concentration and spectrum of pollutants in an urban atmosphere.

To use the differenciation made by Prof. Bates between the "state of the science" and the "state of the art" how should this double information be used in the "state of the art" context for the protection of human health from environmental pollution?

BATES (Canada)

To answer Dr. Berlin's question, there are at least three conclusions:

1. Sampling and measurement of O_3 and SO_2 must be synchronous.

2. Environments which already have considerable concentrations of either SO_2 or O_3 must be very careful that they do not acquire the other.

3. Epidemiological studies must include measurements of pulmonary function of children before and after exercising in these environments, as measured decrements are likely to be the basis of standard setting.

There are at least another three conclusions, of which one is the necessity of further studies of lower concentrations of the two gases together. I do not know the lowest concentrations of the two gases together which might have a significant effect.

WEIR (U.S.A.)

The response by Dr. Bates as well as my response to earlier questions satisfactorly answers these comments.

EMERGENCY POPULATION EXPOSURE: A METHODOLOGICAL APPROACH

(WITH A REPORT ON A HUMAN EXPERIMENT WITH CHLORINE)

P. E. JOOSTING[+] AND M. M. VERBERK[++]

+ TNO Research Institute for Environmental Hygiene, Delft, The Netherlands

++ Coronel Laboratory, Faculty of Medicine, University of Amsterdam, The Netherlands

ABSTRACT

A philosophy on public emergency exposures and the need for public emergency limits (PEL) is presented. PELs can be used for the purpose of planning settlements, storages, transport, organizational measures, etc. PELs apply to tolerable short term emergency exposures of the general population which is neither homogenous in its composition, nor in its responses upon foreign agents. The criteria, used in setting PELs are discussed, with special attention to the more susceptible part of the population, as well as the question whether there exist objective physiological criteria that could be indicative for the population group at highest risk.

A report is given on an experiment with human volunteers that aimed at checking up a postulated tentative PEL for chlorine. Eight subjects, aged 28 - 52, were exposed for two hours to 0.5, 1, 2 and 4 ppm. VC, FEV and FIV measurements before and after showed no significant differences. Subjective phenomena, recorded with 15 min. interval, showed individual, time and concentration dependent characteristics, as well as frequency distributions to which arbitrary tolerance criteria could be applied.

The problem of extrapolating the findings to susceptible subjects and the use of a "safety" factor is discussed. The elaborated PEL value of 1.5, 1 and 1 ppm chlorine for 0.5, 1 and 2 hours respectively, complies with comparable PELs from abroad, but is not consistent with the very small number of literature data that pertain specifically to subjective responses during short term exposures to moderate concentrations of chlorine.

1. PHILOSOPHY

1.1 Introduction

In areas with high population density, industry, storage and transport of dangerous materials, a growing need exists for knowledge about the medical consequences of unforeseen sudden exposures to toxic substances during accidental release of gases and volatile material from tank bursts, traffic collisions, fires etc.

So it is not surprising that in The Netherlands, with an average population density of 396 per square kilometer, a Committee for Prevention of Disasters by Hazardous Substances was appointed in 1964. The recommendations to the government are based a.o. on the work of a Subcommittee Toxicity that submits proposals for maximum concentrations of toxic substances that can be tolerated by the general population at short durations of exposure.

The present report dwells on the basic philosophy of public emergency limits and gives an example of an experimental check-up of a postulated limit for chlorine that had to be tested because of lack of uniform and adequate literature data.

1.2 Public Emergency Limits

Emergency exposures have already been a recognized problem in the philosophy of hygiene since AIHA made issues on that topic [1]. Fundamentally emergency exposure limits (EEL) only refer to abnormal and accidental working conditions, and single exposures of short duration to one specified substance; the worker's capacity of judging an emergency situation and taking co-ordinated action should not be empeded. Possible unexpected or unknown hypersensitivity is not taken into account. Generally industrial workers are supervised as to their state of health with regard to the work situation.

An analogous philosophy has recently been developed in the USA with regard to protection of the general public in case of unpredictable emergencies in which toxic substances are released, in an uncontrolled manner at unpredictable times and places, as the result of accidents such as damage to transportation equipment or fire in a chemical-storage facility [2].

The NAS-NRC document outlines a philosophy that practically parallels the ideas of the Dutch Subcommittee Toxicity. In the following, some aspects will be touched upon that have rendered difficulties in the practice of the elaboration and the implementation of public emergency limits (PEL).

The main purpose of recommended PEL's is serving the planning of industrial settlements, storage, processing and transport of toxic substances; planning of residential areas; revaluation of existing situations and development of technical and organizational measures in potential emergency cases.

It is reasonable to assume that for the greater part of the accidents, referred to in the above, the atmospheric concentrations of the hazardous substance will have reached their maximum and have dropped again within two hours, e.g. as a sequel of measures that have been taken in the meantime. For this reason PEL values, as they have been worked out, apply to exposures of maximally two hours. Additionally, limits for half an hour and one hour are given, too. For seven substances of the list, dealt with by the Dutch Subcommittee, PEL's have been published [3].

1.3 Choice of Criteria

The prime dilemma in the issuance of PEL is the question to what extent a given effect may be regarded as tolerable under emergency conditions. Without doubt there will be a common consent that the following three criteria must be appreciated as unacceptable:

a - increased mortality

b - symptoms and signs of illness, either caused or aggravated by the exposure, which are irreversible or only reversible by intervention, or slowly reversible (more than one or two days).

c - effects that impede self control or co-ordinated and adequate action.

The following two criteria reflect the degree of health impairment that could be tolerated in a population under accidental conditions:

d - symptoms of sickness that appear to be quickly reversible or that are of a mild character.

e - serious discomfort that, how unpleasant it may be, quickly disappears after cessation of the exposure.

As to the items c and e it should be observed that a strong smell or irritation of the mucous membranes of eyes and respiratory tract may give rise to a severe anxiety and fear among a non-accustomed and disquieted population. This may lead to panic, disturb co-ordinated action, and cause secondary injury.

1.4 The General Public as a Target

One of the problems most difficult to overcome is the fact that the general population in a given set up essentially represents a composition of sex, age, endogenous factors, intrinsic liabilities, explicit ill conditions and other variations of human health parameters. There are small children, weak people, pregnant women, subjects suffering from respiratory diseases, cardiac impairment, aged people, etc. If one would try to protect at least the greatest part of those who on the above grounds are expected to be intrinsically more prone to fall a victim under definite emergency conditions, one should recognize the fact that each population comprises about ten to twenty percent weak people for whom a special estimate should be made as to what can be afforded from them. It is logic that PEL values for the general public will be substantially lower than EEL values for workers in industry under medical supervision.

In every population there will be a number of hypersusceptible, exceptionally vulnerable individuals, like people with a serious stage of chronic bronchitis, pneumonia, cor pulmonale, myocardial infarction, asthma and comparable conditions, of whom it is hardly possible to predict in which way and to what extent they will react upon sudden and outspoken changes in atmospheric quality. Despite the voluminous epidemiological literature available, it is very difficult to give an appropriate estimate of this part of the population that cannot be taken into account in a concrete evaluational procedure. Van der Lende [4] states that in the age group 40 to 64 about 8 percent are affected by chronic nonspecific lung disease (CNSLD) to such a degree that, in his opinion, regular treatment is required. He estimates about 1 to 2 percent to be badly handicapped. Personal communications by other lung physicians indicate a smaller part of the population to be in such a stage of illness or hypersusceptibility that their reactions upon inhalation of a foreign gas can never be predicted. Their estimate would be between one and five per thousand of a population at risk. Additionally Van der Lende remarks that exogenous factors (urbanization, air pollution) seem to have less effect on airway obstruction than on productive cough.

There is one feature that could receive special attention. It is the hyperreactivity of the airways as reflected by the results of a histamine threshold test (VC or FEV decrement more than 10 percent upon inhalation of a histamine solution of 8 or 4 mg/ml or less). For some population groups the distribution of histamine thresholds are known [4].

If one would know any existing relationships between the response of volunteers to defined exposures and their histamine sensitivity, it could be possible to make an estimate of reactions among the general public on the basis of the histamine threshold distribution. It would be desirable to have at hand for these purposes a standardized group of volunteers who reflect to a large extent the endogenous factors that may be responsible for the reaction upon an agent. According to our opinion experimentation with people with an explicit clinical condition (bronchitis etc.) does hardly comply with current thoughts in medical ethics.

1.5 Other aspects

Whereas the subject of PEL is still in a more or less developmental stage, a number of topics are rather relevant but cannot be discussed here. Some of these have already been touched upon in another publication [3], as there are incompleteness of adequate literature data; safety factor in extrapolations from "healthy subjects" to "general public" and from animals to human beings; and qualification and quantification of the risks if a PEL still would be exceeded.

2. CHLORINE EXPERIMENT

2.1 Introduction

When the Subcommittee Toxicity tried to elaborate a PEL for chlorine, the adequate available literature data were so scarce and displayed on the other hand such a diversity of dose-effect relationships that it was felt a need to check the tentatively postulated PEL by human experiments.

Whereas the Subcommittee is of the opinion that its responsibility implies that PEL values, postulated with regard to the general public, at least must be acceptable for its own committee members, it was decided to set up a small experiment to check whether a tentatively elaborated PEL of 0.5, 0.3, and 0.3 ppm for 0.5, 1, and 2 hours exposure respectively would stand. These values were based upon experimental work by Beck [5] and Rupp and Henschler [6]. Their young and healthy volunteers were exposed for 30 minutes to 0.02 to 0.9 ppm chlorine. Although their results manifested a broad variance in perceptions, it seemed prudent to assume that 0.5 ppm during 30 minutes would be a limit to subjects with sensitive mucous membranes.

Further the Subcommittee liked to be convinced that at the postulated PEL exposures no trivial respiratory function disturbances would occur. Therefore the study at issue was not limited to subjective feelings only.

2.2 Materials and Methods

Eight subjects, aged 28 to 52 and all members of the Subcommittee, were available. Some were not able to attend all sessions. With one week interval, twice a day a group of 4 subjects was exposed during two hours to 0.5, 1, 2 and 4 ppm chlorine respectively. Because of a technical failure one run with 4 ppm had to skipped so that information on only three persons is available. One of these did not sit out the two hours.

During the exposure the persons were seated in a chamber of 4 x 2.5 x 2.5 cubic meters (a small lock-space included). The test gas perfused the chamber at a rate of 100 cubic meters per hour. Mixing was ideal.

Chlorine gas was generated electrolytically from a saturated and soured NaCl solution. Concentrations inside the chamber were monitored by means of an instantanuously reading coulometric detector. The concentrations remained constant within a range of ± 5%, although the test persons entered and left the chamber at 15 minutes interval to facilitate physiologic tests before and after the exposure.

The latter included: a) ECG and b) breathing frequency in rest over two minutes, and c) spirometry (Pulmotest-Godard): VC, FEV, and FIV. During the exposure a) and b) were also recorded with intervals of 30 minutes.

Each person recorded his subjective feelings qualitatively and quantitatively according to a checklist of symptoms, making use of an absolute and a relative scale of qualifications: 0= no sensation; 1= just perceptible; 2= distinctly perceptible; 3= a nuisance; 4= offensive; 5= unbearable; and + is increasing; - is decreasing; = is constant.

2.3 Results

2.3.1 Heart rate

Although the ECG readings displayed a wide range of individual heart rates, two interesting observations can be made.

Before the first experiment the average heart rate was 87 as people were not yet accustomed to the situation. At the three other runs (with higher concentrations) the before-exposure rates were 72, 72, and 77; i.e. significantly lower (sign test, $p < 0.05$). After 15 minutes of exposure the heart frequency in the first experiment had dropped to 77 already.

During the exposures the heart frequencies stayed rather constant with non-significant differences between the four runs.

The second remarkable phenomenon was observed after cessation of the tests. The mean heart rates, recorded within the first minutes after leaving the chamber, dropped to 66, 64, 64 and 64 respectively. In each case the individual heart rates after exposure were lower than the mean rate during the session ($p < 0.05$).

Although real basic heart rates for each individual were not known, it is probable that the group showed an "off" effect at cessation of the trial, independent of the concentrations during exposure. Question remains whether this may be explained only on account of the mental stress exerted by the test situation, or might reflect a vegetative response upon cessation of a physical stimulus that triggers autonomic regulatory mechanisms.

2.3.2 Rate of respiration

The respiration rate, as recorded before, during, and after the trial did not show anything of special interest: no changes over time and no influence of concentration, neither with regard to the individual values, nor the group means, could be observed.

2.3.3 Spirometry

Comparison of measured VC, FEV and FIV before exposure with the readings after the trial, did not yield remarkable changes. At neither concentration an important decrease could be detected. Only FEV gave a small decrease of 90 ml if all readings were pooled (S.D. 180 ml!) at a significance level of $p < 0.01$ (sign test). But there was no demonstrable association between decrease of FEV and magnitude of the concentration. Neither did individual readings reveal a consistent personal reaction pattern.

It can therefore be postulated that exposure to 0.5, 1 or 2 ppm chlorine, during 2 hours does not result in significant changes of ventilatory capacity among healthy subjects. The 4 ppm experiment did not allow a conclusion (only 2-3 subjects).

2.3.4 Subjective phenomena

The 6-8 subjects recorded every quarter their responses for ten sensations, resulting in a maximum of 64 fifteen-minutes readings per item. These could be arranged as mean scores per quarter of an hour to demonstrate the dynamics of responses during the course of the exposure. Graphical presentation and group mean scores over two hours would allow to compare response patterns with regard to concentration. This has been done in figures 1-6 for the exposures with 0.5, 1, and 2 ppm chlorine (the data of the 4 ppm experiment were too incomplete to allow comparison).

2.3.4.1 Smell (Fig. 1)

Initial perception of smell is about the same for the three concentrations. There is a tendency towards decrease of sensation, particularly during the first hour. Individual differences of scoring between the

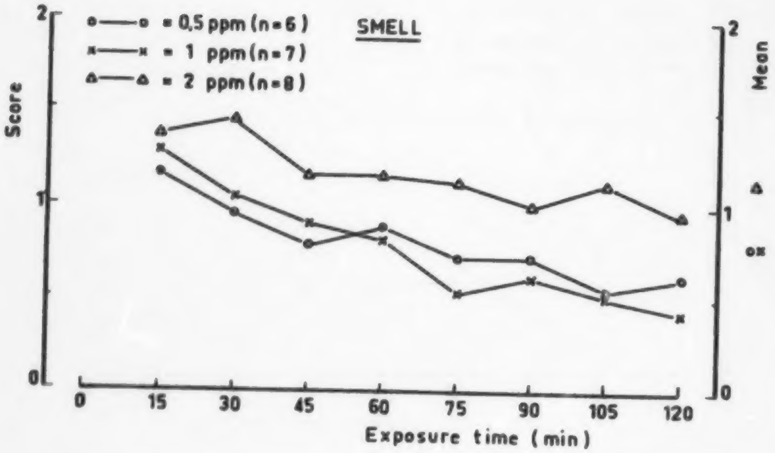


Figure 1 Smell perception - Course of mean scores during the experiments; means over the 2-hr exposure at the right.

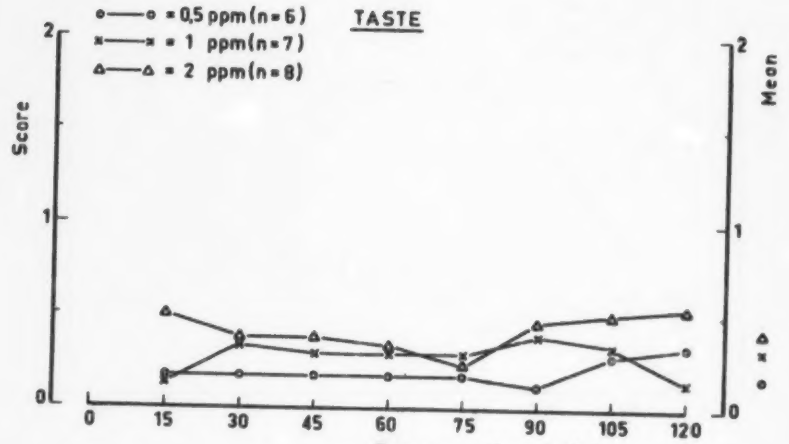


Figure 2

Taste perception - Course of mean scores during the experiments; means over the 2-hr exposure at the right.

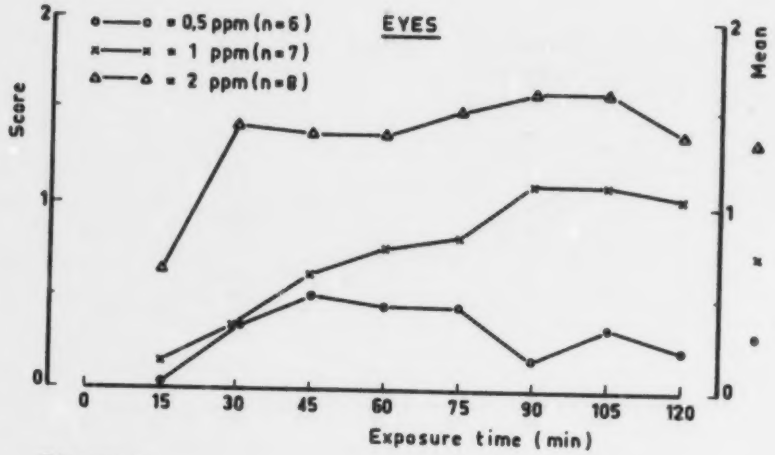


Figure 3

Eye irritation - Course of mean scores during the experiments; means over the 2-hr exposure at the right.

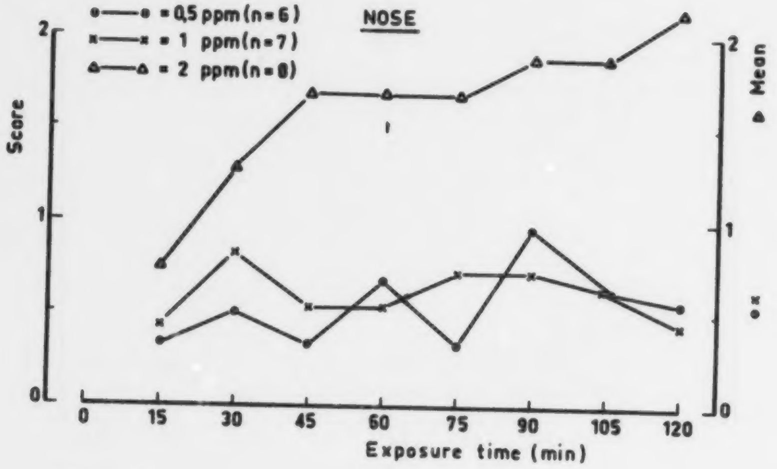


Figure 4

Nose irritation - Course of mean scores during the experiments; means over the 2-hr exposure at the right.

subjects remained consistent over the concentrations.

2.3.4.2 Taste (Fig. 2)

Scores were low, more than half of the test subjects did not perceive anything. There was a consistent individual response pattern.

2.3.4.3 Eye irritation (Fig. 3)

Concentration has a clear-cut influence on eye irritation. While at 0.5 ppm, individual scores remained between 0 and 1, they figured between 0 and 2 at 1 ppm. At 2 ppm three subjects recorded 3 with hardly any momentary 0 code. The gradient of the line at 1 ppm was due to a few subjects who turned out more "responsive" than the others, with an interindividual consistency over the concentrations.

2.3.4.4 Nose irritation (Fig. 4)

No differences can be observed between 0.5 and 1 ppm. At 2 ppm there is a sharp rise during the first hour and to a less degree in the second hour, scores then reading 1-3. At 4 ppm the gradient of the first hour was still steeper.

2.3.4.5 Throat irritation (Fig. 5)

The scores demonstrate a definite association with the concentration level, a.o. reflected by an increasing number of subjects scoring >0. Curiously enough, the person with the highest scores, recorded 0 during the first hour at all three concentrations. The scores at 4 ppm were still higher than at 2 ppm. Individual consistency could not well be observed.

2.3.4.6 Cough (Fig. 6)

Irritation of the airways, resulting in coughing, was experienced by only a few subjects. At 2 ppm three of eight responded. At 4 ppm two of the three subjects scored nuisance. These two were the same who already had reacted at 1 and 2 ppm. There seems to exist a consistency of response.

2.3.4.7 Other phenomena

Headache was experienced by some subjects, generally at the end of the exposure. There were indications for individual consistency.

Perception of chest irritation was observed by one subject at three concentrations. At 4 ppm one out of the three responded with code 1.

Other signs of unfavourable influences upon the well-being of the subjects were not be observed by themselves.

2.3.4.8 Intercomparison of phenomena

In Fig. 7 mean group scores, ranges of individual means and individual maximum readings are presented.

At 0.5 and 1 ppm all the group means were below the level of just per-

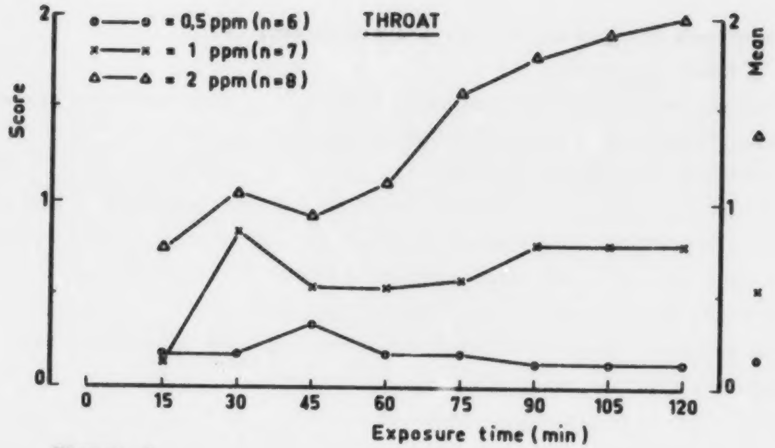


Figure 5

Throat irritation - Course of mean scores during the experiments; means over the 2-hr exposure at the right.

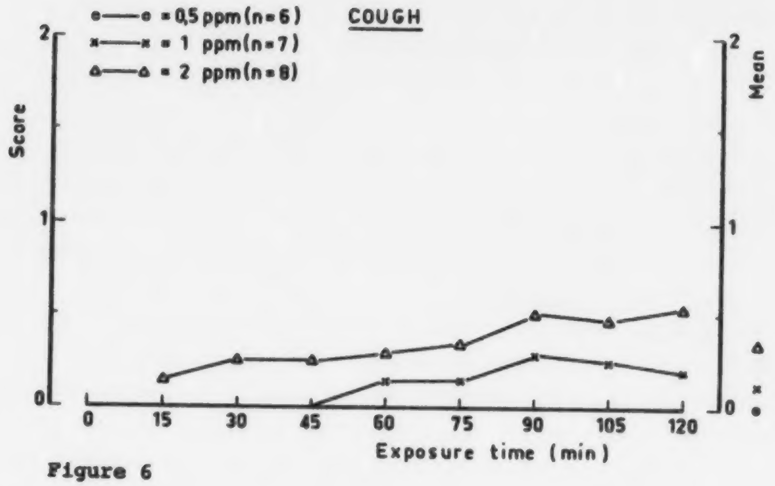


Figure 6

Cough - Course of mean scores during the experiments; means over the 2-hr exposure at the right.

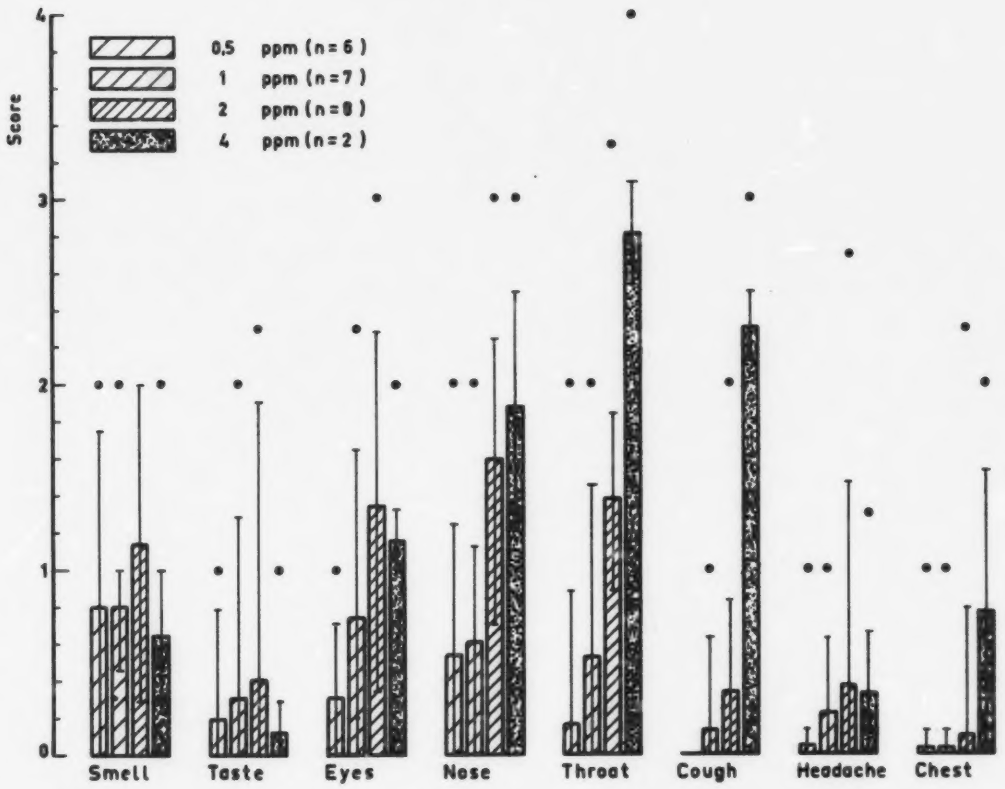


Figure 7 Mean scores (height of columns), lowest and highest individual means (├──┼──┤), and incidental maximum scores (●) in exposures of two hours.

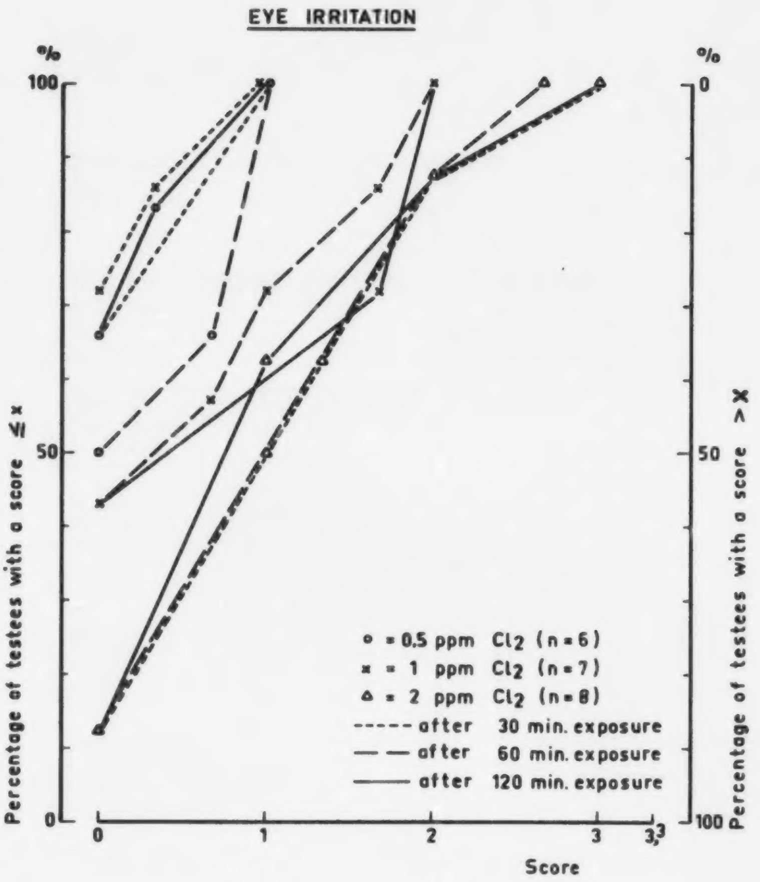


Figure 8 Eye irritation - Cumulative frequency distribution of individual scores at three times of exposure to three concentrations.

ceptible (code 1), and the individual means figured below distinctly perceptible (code 2). At 2 ppm the group means for smell, eye-, nose- and throat-irritation increase above the level of minimum perceptibility. The highest individual means figure about code 2, while incidentally nuisance (code 3) is recorded.

At 4 ppm particularly irritation of nose and throat, and coughing increase in intensity. Some other symptoms tend to diminish. The latter tendency is probably associated with an increased secretion by mucous membranes of nose and eyes as was observed by some subject: rubbing one's eyes increased the irritation. To prevent extra irritation of the throat and coughing, one did not speak or laugh during the second half of the experiment. All three, of whom one performed only 75 minutes, experienced the exposure at 4 ppm as a limit, mainly because of irritation of the throat.

2.3.4.9 Presentation in frequency distributions

To get an impression about the variation of individual scores, cumulative frequency distributions were made of the readings at definite intervals, which reflect the momentary condition of the group after 0.5, 1, and 2 hours of exposure. Figures 8 - 10 display such distributions for eye-, nose- and throat irritation.

With increasing concentration or exposure time, the lines shift to the right, reflecting an increase of response by level or by number of reacting subjects.

The graphs display the phenomenon that in several instances where the group mean score (50 percentile) levels at code X, there may exist a rather large percentage (35 - 40%) with readings up to code (X + 1), whilst 10 - 15% even reach at a level of code (X + 2). Although the number of test subjects was too small to be representative in any respect, this distributional phenomenon should be taken into account seriously when discussing the acceptability of PEL for a population as a whole.

2.4 Criteria and elaboration of a PEL for chlorine

The present investigation has not produced any evidence that a 2-hour exposure to 2 ppm chlorine would have deleterious effects on heart rate and breathing frequency. Apparently these objective parameters do not limit the acceptability for the eight persons under investigation.

From the point of view of checking the PEL values, postulated by the Subcommittee, this finding is reassuring and suggests the possibility of a somewhat higher PEL value for chlorine.

If one would elaborate criteria for acceptability from subjective findings, the frequency distributions of paragraph 2.3.4.9 could serve as a tool to estimate and fix tolerance levels based on the percentage of a population that one would allow to suffer from a definite inconvenience.

To exemplify this by means of a theoretical model, it is imaginable to postulate that under emergency conditions it could be tolerable if 50 per cent of the subjects would perceive the agent in terms of just perceptible (code 1), 35 per cent would record more distinct sensations (code 2), 12 per cent would be bothered by a real nuisance (code 3), whilst 3 per cent would be allowed to suffer from any still more troubling experiences.

Such a procedure is displayed in Fig. 11. The guide is drawn according to the above mentioned percentages of tolerance. Some of the frequency distributions, as presented in Fig. 10, have been brought up in the same diagram: Throat irritation showed to have the best discriminating power between the various exposures and was one of the main arguments of the tested subjects to estimate 4 ppm a limit.

According to the guide-line model, an exposure to 2 ppm chlorine during two hours would not be acceptable because not 50 per cent, but 75 per cent of the people experience more than code 1, and 25 per cent instead of only 15 per cent are bothered by a nuisance (code 2). The frequency distributions of the two other dose-response relationships are acceptable.

Although this principle might be correct, a number of incertainties remains. The number of subjects was small. A true upper level of unbearable (!) exposures has not been set. The subjects were motivated and were familiar with the situation. They were under medical supervision and were aware of the finiteness of the experiment. They could leave the chamber when they wanted. Accordingly their tolerance will have been greater than might be expected for the general public during an emergency. In addition health of the test subjects was good and certainly not representative for the general population.

If one assumes that about 20 per cent of a population is in a condition of reduced resistance (asthma, chronic bronchitis, emphysema, cardiac distress, pregnancy), one might expect that these would represent the tail of a frequency distribution. Even more complicating is the fact that the healthy part of the population (cf. the group of test subjects) may display a broad range of responses, upon which the proportion of the above mentioned 20 per cent of sensitive people should be superposed.

As long as it is unknown in which way and to what extent the more sens-

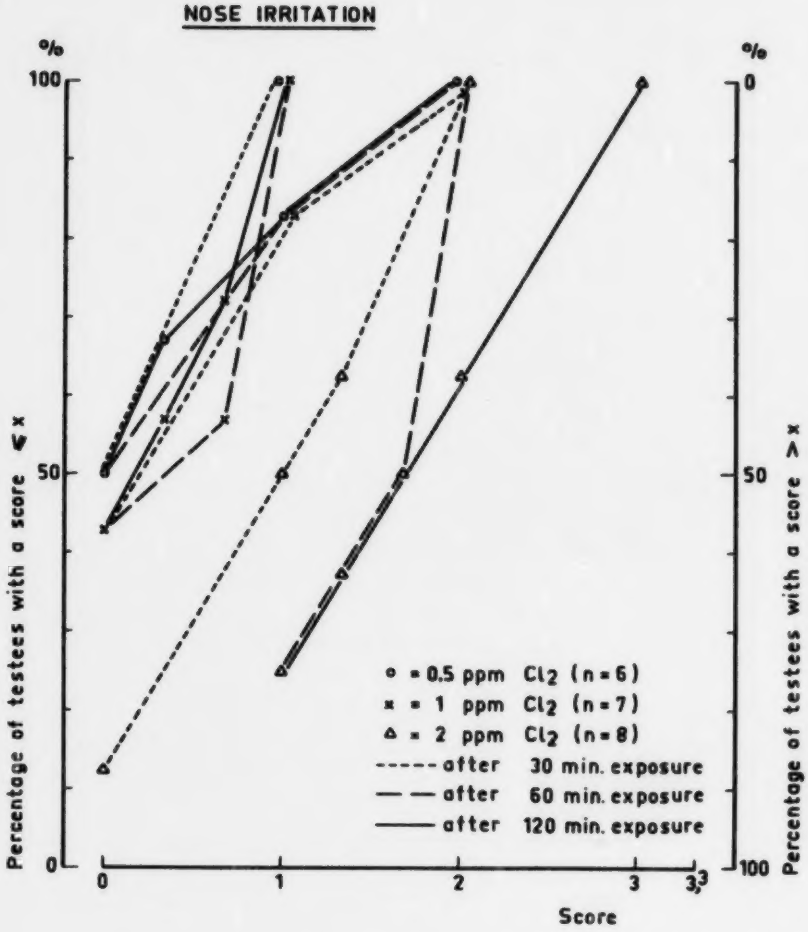


Figure 9

Nose irritation - Cumulative frequency distribution of individual scores at three times of exposure to three concentrations.

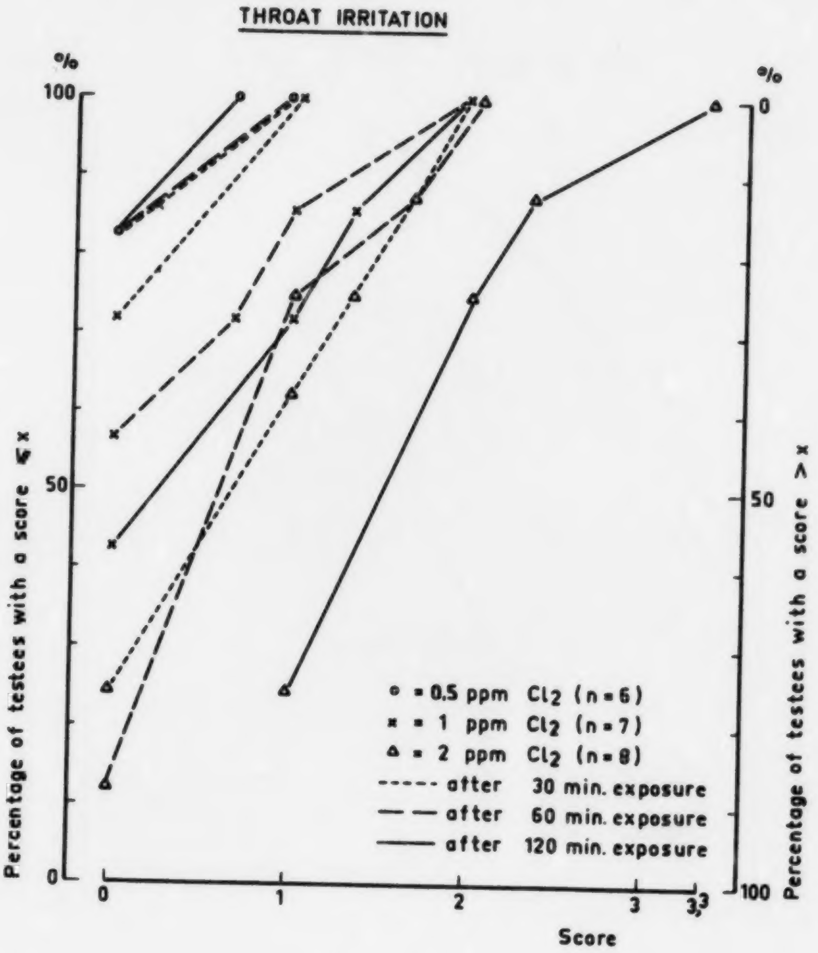


Figure 10

Throat irritation - Cumulative frequency distribution of individual scores at three times of exposure to three concentrations.

itive groups of the general public will react upon short term exposures to the agents for which PEL are required by the authorities, application of a "safety"factor should be used, although this term, admittedly, is a little bit queer in case of emergencies. It seems realistic to divide the concentrations that are associated with a tolerated frequency distribution of symptoms among healthy test subjects, by a factor two, in order to expect that the true frequency distribution of the general population be more or less in line with the experiment.

According to our findings, obviously an emergency exposure of 2 hours to 4 ppm chlorine would not easily be tolerated by non-informed healthy subjects. An exposure of 2 hours to 2 ppm appeares reasonably bearable for healthy subjects.

If this exposure would be appreciated as marginal and a "safety" factor of 2 would be applied, a PEL for the general population would read 1 ppm chlorine for 2 hours. According to the frequency distributions of Fig. 8 - 10 it may be assumed that an exposure of 1 hour to 1 ppm and 0.5 hour to 1.5 ppm would not result in outspoken deleterious effects either.

It should be stressed that extreme susceptibility cannot and has not taken into account.

2.5 Comparison with existing PEL

The NAS/NRC Committee on Toxicology [7] has given PEL values for comparable exposures. Although the philosophy is about the same, the reasoning is not quite clear in the NAS/NRC paper. The more therefore is it interesting that both issues are sufficiently matching. The Pennsylvania Department on Occupational Health [8] has also issued a limit, viz. 3 ppm during 5 minutes, which also fits the overall pattern:

PEL for chlorine (ppm)

exposure time (min.)	5	10	30	60	120
Pennsylvania	3	-	-	-	-
NAS/NRC	-	3	2	2	-
Netherlands	-	-	1.5	1	1

Both American PEL values are in agreement with our findings in the human experiment with healthy subjects. The latter, on the other hand,

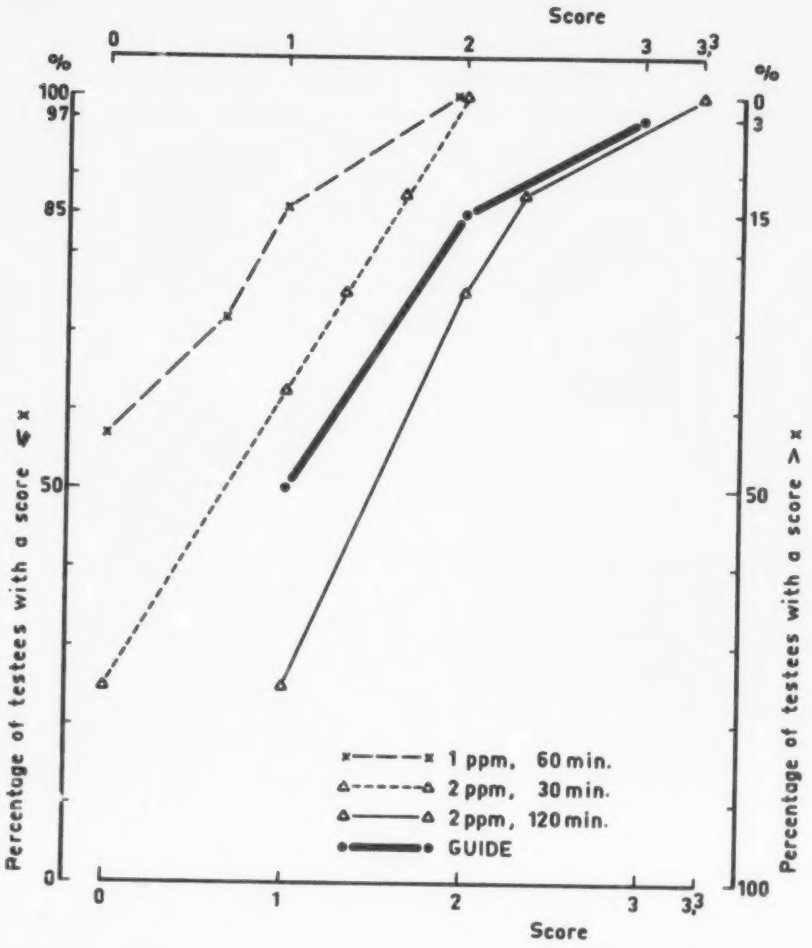


Figure 11 Example of an arbitrary guide for throat irritation.

differ widely from the response patterns found by Beck [8] and Rupp and Henschler [6], who probably have worked with very sensitive and differently motivated volunteers. In our opinion our first tentatively postulated PEL values of 0,5, 0.3 and 0.3 ppm, which were based on their work, must be judged as unrealistically low. On the basis of the underlying study the members of the Subcommittee Toxicology had no difficulties in changing their mind into 1.5, 1, and 1 ppm respectively.

2.6 Final remarks

To develop further methodology for the purpose of elaborating realistic PEL, some more information is needed about:

- qualitative composition of the general public with regard to its sensitivity for irritating gases in general.
- effects among sensitive groups by certain gases.
- relationship between parameters of hyperreactivity (e.g. histamine sensitivity) and response mechanisms on irritating substances in general.
- influence of physical stress (= increased ventilation) on the influence of irritant gases.
- influence of emotional factors, fear and ignorance of the toxicity of the agent.

Research in these fields should be stimulated and co-ordinated.

2.7 Post scriptum observation

Some weeks before the presentation of this paper observations were made that should not remain unrevealed, because they might throw a light on the above mentioned differences between the German findings and our own.

In order to check a PEL for ammonia the subcommittee members exposed themselves in the same manner as to cholrine. Because it was felt a need to check the possible hypertrophy of motivation and the outsposen familiarity with the subject, a group of eight healthy students was selected to participate in the experiment, in separate sessions.

The students turned out to score systematically higher than the committee members had done, for a great number of sensations. An example of extreme differences between the frequency distributions of both groups is revealed for throat irritation in figure 12: the maximum score among the committee members (code 2^+) is lower than the mini-

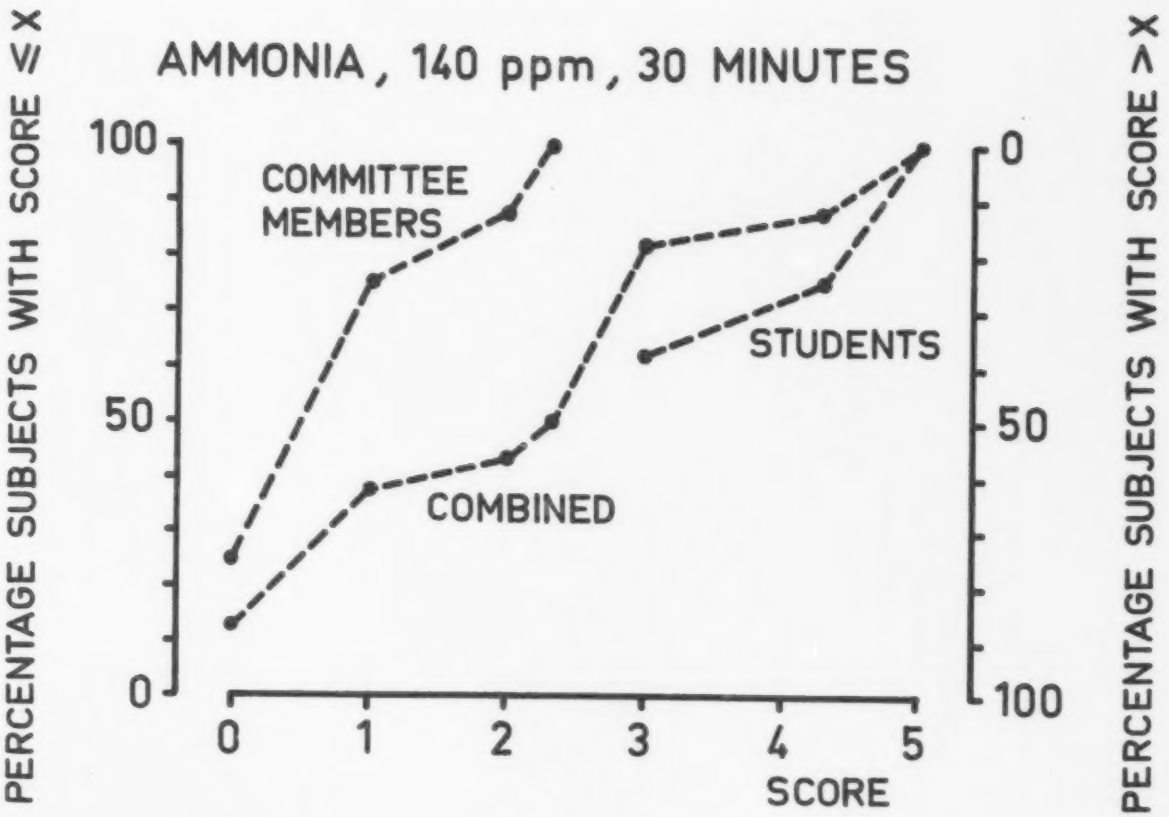


Figure 12

Exposure to ammonia : difference between cumulative frequency distribution of committee members and students mum score (code 3) of the students. Two of the latter (25%) scored unbearable (code 5) after half an hour, already.

If one pools both parties, the result can be illustrated by the combined frequency distribution in the centre of the graph. Effectively this procedure means a big shift to either of the two original distributions. This phenomenon induces questions about the students data and throws doubt on the question whether our group of committee members still is an appropriate panel to test tentatively postulated PEL's.

According to our opinion this observation does not undermine essentially the principle of a phenomenological and experimental approach in the setting of standards, particularly the elaboration of public emergency limits in case of simple irritating substances.

Acknowledgement

The Directorate General of Labour, under the auspices of which the Subcommittee Toxicity fulfils its task, gave a grant for the experiment that was performed in the test chamber of the TNO Research Institute for Environmental Health, medical supervision and physiological tests being performed by Dr. B. Bink, Netherlands Institute for Preventive Medicine TNO, Leyden.

The authors wish to express their special gratitude towards the other members of the Subcommittee who participated as test subjects in the experiment and who were so kind as to allow publication part of the basic philosophy that was developed by the joint effort of present and past members, whose names are: K. Biersteker, A.W.M. Balemans, H. Eilers, M.J. van Logten, J.H. Koeman, T. Rooyakkers-Beemster, E.H. Siccama and R.L. Zielhuis (Chairman).

REFERENCES

1 AMERICAN INDUSTRIAL HYGIENE ASSOCIATION (AIHA), TOXICOLOGY COMMITTEE. "Emergency Exposure Limits", Amer. Industr. Hyg. Ass. J., 25, 578 (1964).

2 NATIONAL ACADEMY OF SCIENCES - NATIONAL RESEARCH COUNCIL (NAS - NRC), Basis for establishing guides for short-term exposure of the public to air pollutants, U.S. Dept. Commerce, Nat. Techn. Inform. Service, Washington DC, (May 1971).

3 SUBCOMMITTEE TOXICITY OF THE DUTCH COMMITTEE FOR PREVENTION OF DISASTERS BY HAZARDOUS SUBSTANCES, "Public Emergency Limits", Staub-Reinhaltung der Luft, 34, 85 (1974).

4 LENDE, R. VAN DER, Epidemiology of chronic non-specific lung disease (chronic bronchitis), Thesis Groningen University, Van Gorkum Comp., Assen, The Netherlands (1969).

5 BECK, H., Experimentelle Ermittlung von Geruchsschwellen einiger wichtigen Reizgase und Erscheinungen bei Einwirkung geringer Konzentrationen auf den Menschen, Inaugural-Dissertation, Würzburg, West-Germany (1959).

6 RUPP, H., HENSCHLER, D., "Wirkungen geringer Chlor- und Bromkonzentrationen auf den Menschen", Arch. Gewerbepath. Gewerbehyg., 23, 79 (1967).

7 COMMITTEE ON TOXICOLOGY OF NAS/NRC, Guides for short term exposures of the public to air pollutants. III.Guide for chlorine, Washington DC, (1973).

8 PENNSYLVANIA DEPT. OF HEALTH, DIVISION OCCUPATIONAL HEALTH, Short term exposure limits, Harrisburg, Pa., (1966).

DISCUSSION

HINE (U.S.A.)

In using human sensory response panels two basic principles are followed by our group. First the panel must be carefully selected by trials to eliminate persons giving false positive response in the absence of stimuli and those failing to give a response where 90% of subjects rate the exposure as + 3 on a 0-5 scale. Secondly the panel must be trained by repeated exposures to the same concentration so that they will have a consistent grading of the degree of irritancy. Of course all exposures after the training sessions at known concentrations are done in a double blind fashion.

JOOSTING (Netherlands)

Thank you for your constructive comment. We were fully conscious about the fact that our method would not stand your criteria. It was not our aim to set PEL's on a scientific basis, but we would check what the impact could be of the postulated PEL for chlorine which we did not yet feel sure enough about. Therefore we started with the low concentration. In the recent experiment with ammonia we kept the procedure of increasing the exposure in the next session on the basis of the findings in the preceding one, but without telling the subjects to what actual concentrations they would be exposed. The students were told that they would be exposed to an irritating agent, without any hazard.

LEFEVRE (Belgium)

Did the patients exposed to chlorine vapours by Dr. Joosting subsequently show dyspnoea or a tendency to pulmonary oedema?

JOOSTING (Netherlands)

From the literature that we had studied before starting the experiments with ourselves, we had not learned that an exposure during 2 hours to e.g. 4 ppm chlorine would result in clinical symptoms like dyspnoea or signs of a tendency to pulmonary oedema. One of us experienced a sensation of irritation within the chest at some moments during the exposure to 2 ppm; but this phenomenon disappeared at cessation of the exposure. No one of us complained about the symptoms you mentioned. If we would have expected such serious effects to happen as a sequel of the well controlled exposure, we would never have started the trial.

L'INFLUENCE DU BRUIT SUR LE SOMMEIL DES TRAVAILLEURS DE NUIT ET DES TRAVAILLEURS PAR EQUIPES ALTERNANTES

P. KNAUTH ET J. RUTENFRANZ

Institut für Arbeitsphysiologie an der Universität Dortmund, BRD

RESUME

Dans le cadre de travail par roulement réalisé en laboratoire, nous avons étudié l'influence du bruit et du travail par roulement sur le sommeil. Le travail par roulement expérimental nous a servi de méthode nous permettant d'étudier l'influence de la combinaison de ces deux facteurs sur le sommeil.

Nous basant sur le résultat d'enquêtes effectuées auprès de travailleurs en équipes alternantes, nous avons perturbé le sommeil des sujets par des bruits de circulation (45-70dB(A)) et par des bruits d'enfants (20-60dB(A)). Pendant le sommeil, nous avons enregistré les EEG, EMG, EOG et ECG ainsi que les mouvements du lit afin de pouvoir déceler les influences du bruit sur le sommeil.

Etant donné que les travailleurs de nuit ne dorment après le travail de nuit en moyenne que 6 heures, nous avons limité le travail de jour de deux des sujets à 6 heures pendant une période de travail de nuit de trois semaines, tandis que deux autres sujets jouissaient d'un sommeil illimité.

La perturbation du sommeil par le bruit ne dépendait pas seulement de l'intensité de ce bruit, mais surtout de l'information qui en ressort. La durée totale du sommeil ainsi que celle du sommeil PMO était en moyenne plus courte quand le sommeil

Preceding page blank

était perturbé par des bruits d'enfants que lors d'une perturbation par des bruits de circulation.

Les paramètres EEG, EOG, EMG et mouvements du lit ne faisaient pas apparaître une habituation au bruit au cours de l'expérience.

La limitation à 6 heures du sommeil de jour, comme on la rencontre habituellement chez les travailleurs de nuit, avait pour conséquence une réduction des phases PMO et IV par rapport au sommeil de jour illimité. En ce qui concerne le pourcentage des stades PMO et IV par rapport à la totalité du sommeil, nous n'avons pas constaté de différence statistiquement significative entre le sommeil limité et le sommeil illimité.

L'évaluation subjective de la qualité du sommeil présentait au cours des trois semaines de travail de nuit un tracé différent de celui des stades de sommeil PMO et IV.

Etant donné qu'en général le sommeil de jour des travailleurs de nuit est plus court et plus perturbé par des bruits que le sommeil normal de nuit, il a été recommandé de ne pas utiliser de plans de roulement comportant beaucoup de travail de nuit consecutif.

ABSTRACT

Shift work was organized in the laboratory to study the effects of noise and shift work on sleep. Experimental shift work served as a means of studying the combined effects of these two factors on sleep.

Using as a basis the results of surveys carried out on shift workers, we disturbed the subjects' sleep by traffic noise (45-

70 dB(A)) and noise made by children (20-60 dB(A)). We recorded the EEG, EMG, EOG and ECG and bed movements during sleep in order to determine the influence of noise on sleep.

As night workers only sleep an average six hours after night work, we limited the day sleep of two of the subjects to six hours during three weeks of night work, while two other subjects enjoyed unlimited sleep.

Sleep disturbance owing to noise did not depend solely on the intensity of the noise, but above all on its information content. The overall duration of sleep and REM sleep was on the whole shorter when it was disturbed by children's noise than when it was disturbed by traffic noise.

The EEG, EOG, EMG parameters and bed movements showed no evidence of inurement to noise during the experiment.

The fact of limiting day sleep to six hours, as is usually the case for night workers, caused a shortening of the REM stage and stage IV compared to unlimited day sleep. As regards the percentage of the REM stage and stage IV in relation to the overall period of sleep, we did not discover any statistically significant difference between limited and unlimited sleep.

Subjective assessments of the quality of sleep during the three weeks of night work showed a different pattern to that of the REM stage and stage IV.

In view of the fact that the day-time sleep of night workers is shorter and disturbed by more noise than normal night-time sleep, it has been recommended that work schedules involving a lot of successive night work should not be used.

1. Introduction

Un des problèmes essentiels du travailleur en équipes alternantes est le sommeil. Dans une étude précédente (fig. 1) nous (KNAUTH et al. [1]) avions, dans le cadre de travail par équipes en laboratoire, comparé premièrement le sommeil de jour au sommeil de nuit, deuxièmement le sommeil perturbé au sommeil non perturbé. La fig. 1 représente quatre exemples de sommeil d'un même sujet. Nous avons constaté ces mêmes tendances chez les autres sujets. Le dessin du haut représente le sommeil de nuit sans aucune perturbation d'un sujet dormant dans une chambre insonorisée. Pendant la nuit perturbée par des bruits (second dessin), la durée du sommeil est plus brève, l'image générale est plus morcelée et le stade IV en particulier est plus souvent interrompu. Un décalage de phase du sommeil vers la phase de jour donne lieu à un racourcissement supplémentaire du sommeil. Les conditions de sommeil de jour avec perturbations sonores sont particulièrement défavorables, car il en résulte un déficit important de sommeil par rapport au sommeil de nuit non perturbé.

Nous nous sommes donc demandés quels étaient les effets sur le sommeil de jour d'un travail de nuit de plusieurs semaines : est-ce qu'il en résulte une accumulation du manque de sommeil, ou bien est-ce que le corps humain peut compenser ce manque de sommeil ? Cette question ne pouvait être étudiée que dans le cadre d'un cycle d'expérience de travail par roulement d'une longue durée. Etant donné que de telles expériences de plusieurs semaines nécessitent beaucoup de personnel et de temps, il n'existe - à notre connaissance - pas encore d'étude comparable.

2. Méthode

Quatre sujets de sexe masculin agés de 22 à 25 ans ont vécu 5 semaines chacun à l'Institut. A une semaine de travail de jour succédaient trois semaines de travail de nuit et une semaine de repos sans travail. Deux des sujets pouvaient dormir autant qu'ils le voulaient après le travail de nuit. Nous avons limité le sommeil après le travail de nuit des deux autres sujets à 6 heures, puisque des enquêtes auprès de travailleurs de nuit ont révélé une durée moyenne de sommeil de 6 heures.

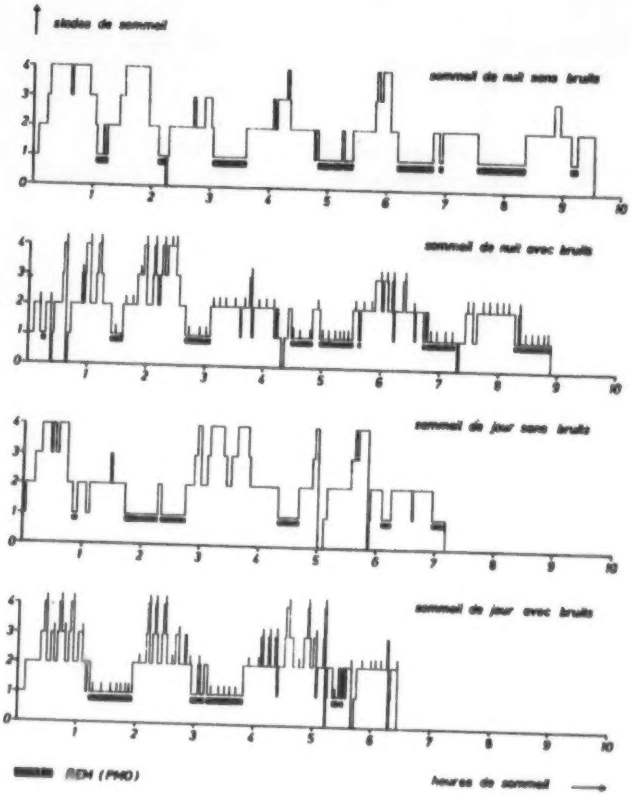


Fig. 1 Stades de sommeil d'un sujet

Les sujets dormaient dans une chambre insonorisée. La partie gauche de la fig. 2 représente un sujet couché dans un lit dans la chambre insonorisée. La fréquence du pouls et la température du corps étaient enregistrées pendant le sommeil et continuellement pendant la totalité de l'expérience. De plus, les enregistrements suivants étaient effectués pendant le sommeil :

2 EEG (potentiels electroencéphalographiques)
1 EOG (potentiels oculaires)
1 EMG (tonus musculaire)
mouvements du lit

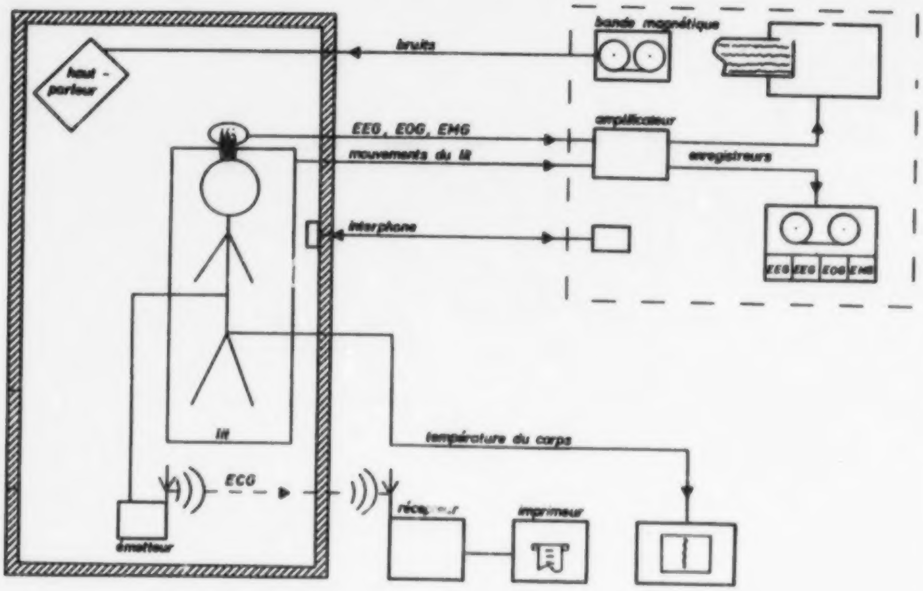

haut-parleur
bruits
bande magnétique
EEG, EOG, EMG
mouvements du lit
amplificateur
enregistreurs
interphone
EEG
EEG
EOG
EMG
lit
température du corps
ECG
émetteur
récepteur
imprimeur

Fig. 2 Disposition expérimentale

Nos enquêtes (KNAUTH et al. [2], RUTENFRANZ et al. [3]) ayant révélé que le sommeil de jour des travailleurs de nuit est perturbé la plupart du temps par le bruit causé par la circulation et par les enfants, nous passions alternativement des enregistrements de ces deux genres de bruit pendant le sommeil dans la chambre insonorisée. Tandis que les bruits d'enfants variaient fortement dans leur intensité entre 20 dB(A) et 60 dB(A) environ (fig. 3), l'intensité des bruits de circulation restait relativement constante entre 45 dB(A) et 70 dB(A) (fig. 4). Le bruit standardisé était passé à l'aide d'un magnétophone et par l'intermédiaire d'un haut-parleur environ toutes les 8 minutes pour une durée de 3 secondes dans la chambre. Les effets de ce bruit sur l'EEG, l'EOG, l'EMG et sur les mouvements du lit étaient enregistrés. A la fin du sommeil, les sujets remplissaient un questionnaire par lequel on leur demandait d'évaluer leur dernier sommeil.

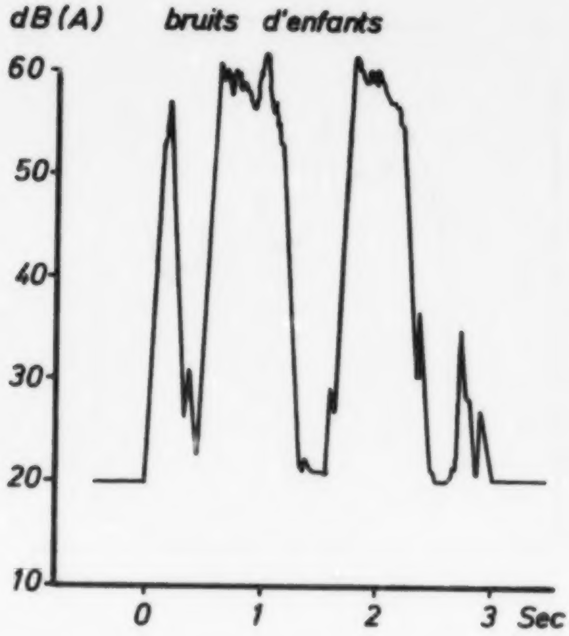


Fig. 3 Intensité des bruits d'enfants

Pendant les heures de travail, les sujets devaient effectuer à l'Institut un travail de montage à une place de travail industrielle. Le travail était interrompu à intervalles réguliers (toutes les 2 heures 1/2) pour 25 minutes environ. Pendant cette interruption, on mesurait la vitesse de réaction des sujets à l'aide d'un appareil à choix multiple. En outre, les sujets devaient témoigner de leur forme ressentie subjectivement en remplissant un questionnaire scalaire. Nous recueillions enfin à intervalles réguliers des échantillons de l'urine des sujets pour en définir ensuite le taux en catécholamines et en électrolytes.

Les stades de sommeil ont été déterminés de façon visuelle d'après RECHTSCHAFFEN et KALES. Ils ont de plus été comparés aux résultats d'une analyse de sommeil automatique (développée par GAILLARD [4]).

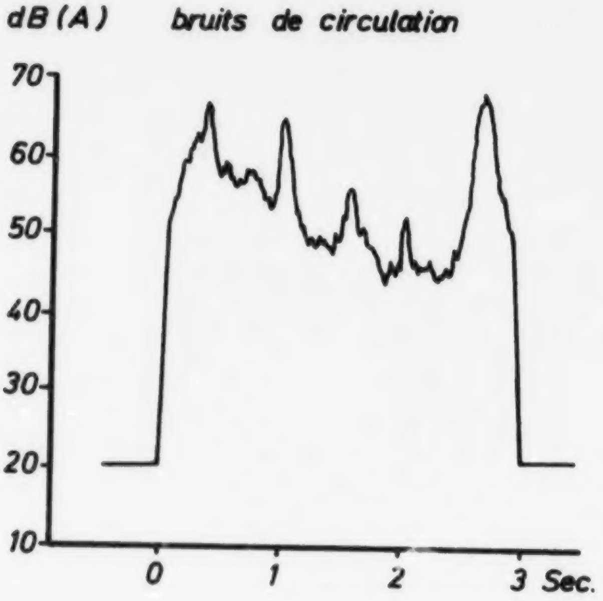


Fig. 4 Intensité des bruits de circulation

Je voudrais ne présenter ici que quelques-uns des premiers résultats se basant sur le dépouillement des enregistrements objectifs du sommeil et sur l'évaluation subjective du sommeil de jour au cours des trois semaines de travail de nuit.

3. Résultats

Les différents paramètres du sommeil témoignent d'une forte instabilité interindividuelle et intraindividuelle. Il est toutefois possible d'y reconnaître certaines tendances.

Comme nous avions perturbé le sommeil alternativement un jour par des bruits de circulation et l'autre jour par des bruits d'enfants, nous étions en mesure de comparer les différents effets de ces deux genres de bruit. La fig. 5 représente la

durée moyenne du sommeil de jour des deux sujets auxquels nous permettions de dormir sans limitation. Le sommeil perturbé par des bruits de circulation durait en moyenne 490,9 minutes. D'une façon statistiquement significative ($p < 0,001$), il durait plus longtemps que le sommeil durant lequel nous introduisions des bruits d'enfants dans la chambre. (338,7 minutes).
La durée du sommeil PMO variait également en fonction du genre de bruit introduit. Les quatre sujets passaient en moyenne 112,6 minutes par sommeil dans le stade PMO lors de la perturbation par bruits de circulation, tandis que la durée du stade PMO dans le cas de bruits d'enfants n'était que de 72,6 min ($p < 0,01$). Si toutefois on rapporte le sommeil PMO au sommeil total, on ne constate pas de différence significative entre la proportion des stades PMO en cas de bruits de circulation (24,2 %) et celle des stades PMO en cas de bruits d'enfants (20,4 %). Le sommeil profond a été perturbé presque aussi fortement par les bruits de circulation (43,4 min) que par les bruits d'enfants (37,5 min).

Nous avons analysé les réactions au bruit, telles qu'elles ressortaient des EEG, EOG, EMG et des mouvements du lit. Aucun indice d'habituation éventuelle n'a pu être relevé. Par contre, les protocoles d'expérience révélaient que tous les sujets déclaraient s'être habitué au bruit au bout de quelques jours.

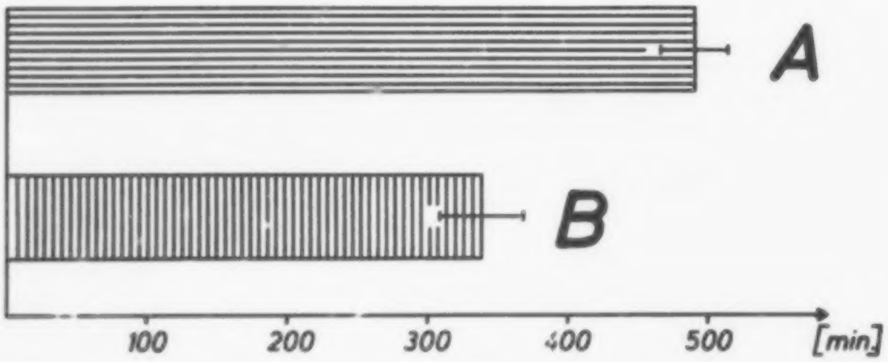


Fig. 5 Durée moyenne du sommeil de jour perturbé par des bruits de circulation (A) ou des bruits d'enfants (B)
($\bar{x} \pm \varepsilon_{\bar{x}}$; $p < 0,001$)

La fig. 6 représente des exemples de sommeil d'un sujet qui pouvait dormir sans limitation. Les trois dessins du haut montrent un raccourcissement progressif du sommeil, en partant du sommeil de nuit sans bruit, en passant par le sommeil de nuit avec bruit et en allant jusqu'au premier sommeil de jour avec bruit. Pendant la période de travail de nuit (1er, 9ème et 19ème jour, fig. 6), la durée du sommeil augmentait de nouveau. Toutefois deux des sujets n'avaient pas la possibilité de déterminer la durée du sommeil à leur gré durant la période de travail de nuit.

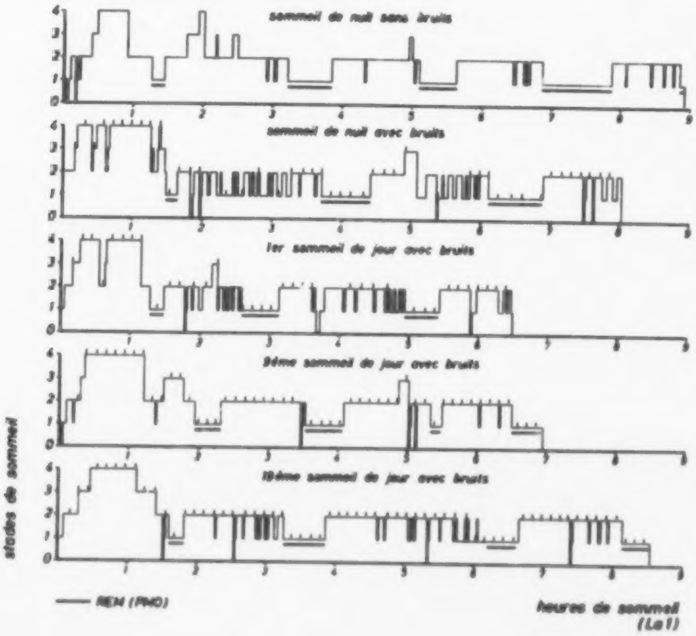


Fig. 6 Stades de sommeil de deux nuits et de trois jours d'un sujet

La comparaison du sommeil de jour illimité avec le sommeil limité à 6 heures révélait des différences significatives ($p < 0,01$) dans la durée totale du sommeil profond (fig. 7) et du sommeil PMO. En cas de sommeil illimité, le sommeil PMO durait en moyenne plus longtemps (101,2 min) que dans le sommeil limité (76,2 min). Alors que les sujets passaient en moyenne 43,6 min en sommeil profond en cas de sommeil illimité, le stade IV ne durait en moyenne que 34,5 min dans le cas de sommeil limité. Le calcul du pourcentage des stades PMO et IV de la totalité du sommeil n'a toutefois pas révélé de différences significatives entre le sommeil limité et le sommeil illimité.

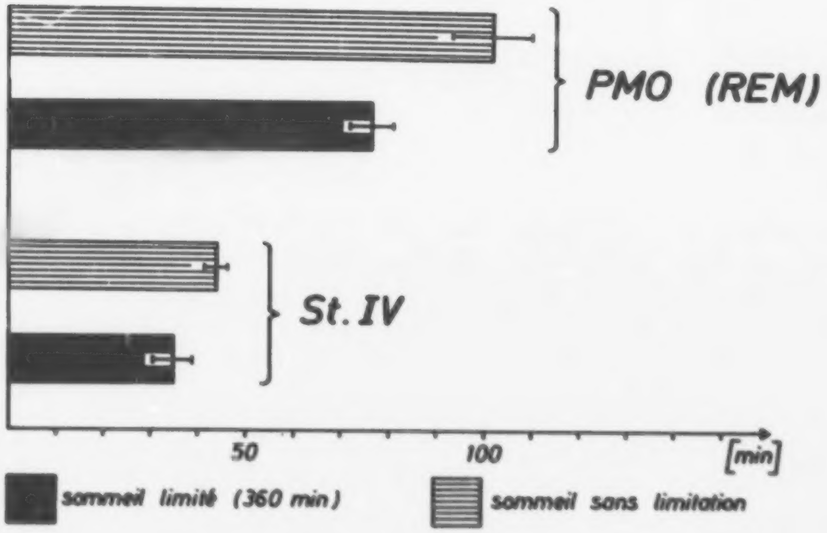


Fig. 7 Durée des stades PMO et IV
pendant le sommeil limité et illimité
($\bar{x} \pm s_{\bar{x}}$; $p < 0,01$)

Il n'existe pas jusqu'ici d'opinion unitaire sur les critères de la qualité du sommeil. On accorde toutefois dans le sommeil un rôle important aux stades IV et PMO. Nous avons donc comparé sur une durée de trois semaines de travail de nuit le pourcentage des stades PMO et IV de la totalité du sommeil à l'évaluation subjective de la qualité du sommeil exprimée par chacun des sujets. Ce n'est que dans quelques cas isolés qu'il était possible de reconnaître une tendance unitaire des trois paramètres. Alors que les deux paramètres objectifs variaient le plus souvent dans la même direction, l'évaluation subjective de la qualité du sommeil témoignait d'une évolution divergeante.

4. Discussion

Il est pratiquement impossible de séparer les effets des deux facteurs : bruit et travail de nuit. Le changement du rhythme de vie consécutif au travail de nuit a dans une certaine mesure une influence sur les nombreuses fonctions du corps humain soumis à un rhythme circadien. Le sommeil se trouve également changé à la suite du décalage des phases des activités, du fait que le cours de chacun des stades est lié à l'heure de la journée.

Le bruit étant en général beaucoup plus fort le jour que la nuit, il faut s'attendre en cas de sommeil de jour des travailleurs de nuit à une réduction de la durée et à une dégradation de la qualité du sommeil.

Dans notre expérience, l'intensité des bruits d'enfants n'atteignait pas la valeur maximale des bruits de circulation. Cependant les bruits d'enfants - sans doute parce qu'ils sont plus variés et plus riches en informations - perturbaient plus fortement le sommeil que les bruits de circulation.

La réduction de sommeil à 6 heures, habituelle chez les travailleurs de nuit, diminuait la durée du sommeil PMO de même que la durée du sommeil profond. Ces déficits n'ont pas été compensés au cours de la période de trois semaines de travail de nuit. C'est pourquoi nous estimons que les plans de roulement où se succèdent plusieurs nuits de travail ne sont pas recommandables.

Bibliographie

1. Knauth, P. und Rutenfranz, J., "Untersuchungen zum Problem des Schlafverhaltens bei experimenteller Schichtarbeit", Internationales Archiv für Arbeitsmedizin, 30, 1 - 22 (1972)

2. Knauth, P. und Rutenfranz, J., "Untersuchungen über die Beziehungen zwischen Schichtform und Tagesaufteilung", Internationales Archiv für Arbeitsmedizin, 30, 173 - 191 (1972)

3. Rutenfranz, J., Knauth, P., Hildebrandt, G. und Rohmert, W., "Nacht- und Schichtarbeit von Triebfahrzeugführern, 1. Mitteilung. Untersuchungen über die tägliche Arbeitszeit und die übrige Tagesaufteilung", Internationales Archiv für Arbeitsmedizin, 32, 243 - 259 (1974)

4. Gaillard, J.-M., Simmen, A.E. et Tissot, R., "Analyse automatique des enregistrements polygraphiques de sommeil", Electroencephalography and Clinical Neurophysiology 30, 557 - 561 (1971)

DISCUSSION

STUPFEL (France)

Pourquoi avez-vous utilisé des bruits d'enfants et non des bruits de circulation ou des bruits d'ateliers?

KNAUTH (République fédérale d'Allemagne)

Nos enquêtes par questionnaire effectuées auprès d'ouvriers effectuant un travail par roulemment ayant révélé que le sommeil de jour des travailleurs de nuit est perturbé la plupart du temps par les bruits de la circulation et les bruits causés par les enfants, nous avons lors des essais perturbé le sommeil des personnes par ces deux genres de bruit.

JANSEN (République fédérale d'Allemagne)

1. Quels étaient les niveaux acoustiques continus équivalents enregistrés lors de vos essais?
(Les valeurs guides mentionnent toujours des niveaux acoustiques continus équivalents)

2. Est-ce que ce sont les niveaux maximaux ou les niveaux sonores constants équivalents qui sont plus importants?

KNAUT (République fédérale d'Allemagne)

1. Nous n'avons pas encore calculé des "niveaux acoustiques continus équivalents".

2. D'après les premiers dépouillements, ce ne sont pas les pointes d'intensité sonore qui semblent avoir joué un rôle plus important mais les variations du niveau de pression sonore et le contenu d'information de bruit. Les bruits d'enfants avec une intensité maximale de 60 dB(A) (figure 3) perturbaient beaucoup plus fortement le sommeil que les bruits de la circulation avec une intensité maximale de 70 dB(A) (figure 4). La durée totale du sommeil, la durée du sommeil REM (PMO) ainsi que du sommeil profond étaient nettement plus courtes quand le sommeil était perturbé par des bruits causés par des enfants que lors d'une perturbation par le bruit de la circulation.

VAN MEIRHAEGHE (Belgique)

Je voudrais avoir quelques précisions sur l'évaluation subjective du sommeil par les sujets et, notamment, si ceux-ci déclaraient par exemple que leur sommeil avait été troublé par des rêves en rapport avec la nature de bruit.

KNAUT (République fédérale d'Allemagne)

A la fin du sommeil, les sujets devaient remplir un questionnaire dans lequel on leur demandait d'apprécier la qualité de leur sommeil, d'indiquer comment ils s'étaient endormis, les perturbations ressenties pendant le sommeil et leur condition personnelle. Les résultats de ces évaluations subjectives du sommeil correspondaient rarement avec les enregistrements objectifs.

Alors que les sujets déclaraient par exemple s'être habitués au bruit au bout de quelques jours, aucun indice d' accoutumance éventuelle n'était décelable dans les enregistrements des EEG, EOG et EMG ainsi que dans les mouvements du lit.

Un sujet a déclaré après une période de sommeil perturbé par des bruits de la circulation avoir rêvé plusieurs fois de bruits d'avion.

CHAMBERS (Irlande)

Il m'intéresserait de savoir comment le stimulus acoustique a été appliqué; est-ce que le bruit a été émis au hasard ou à intervalles spécifiques? Je pose cette question parce que si la fréquence du stimulus correspondait à des périodes de sommeil REM (mouvements oculaires rapides), il se peut que se produise un surcroît de sommeil REM similaire à celui que décrit Dement dans son ouvrage sur la privation de sommeil REM. Même si vous n'avez pas considéré cela comme un phénomène, il devrait vous être possible, en examinant vos notes, de vérifier s'il y a eu coïncidence entre le stimulus et le sommeil REM afin de confirmer ou d'infirmer cette hypothèse et, le cas échéant, d'éliminer cet effet possible.

KNAUT (République fédérale d'Allemagne)

Lors de cette étude nous avons passé un bruit toutes les 8 minutes dans la chambre insonorisée de façon à ce que tous les stades du sommeil soient perturbés. Nous avons choisi ce bruit standardisé et régulier pour placer les sujets dans les mêmes conditions d'essai. Toutefois, nous envisageons pour nos essais futurs de perturber également le sommeil par des bruits presentés au hasard.

Jusqu'à présent, dans nos essais, la durée totale du sommeil REM a toujours été nettement plus courte dans le cas d'un sommeil perturbé que dans celui d'un sommeil non perturbé. Si toutefois, on compare sommeil REM au sommeil total, on ne constate pas de différence significative entre la proportion du sommeil REM dans le cas du sommeil perturbé et cette poportion dans le cas du sommeil non perturbé.

KREUZER (République fédérale d'Allemagne)

Se trouvait-il des pères de famille parmi les sujets exposés aux bruits d'enfants?

Ces sujets-là devraient au moins reconnaître qu'ils sont plus sensibles aux bruits d'enfants qu'aux autres bruits de même intensité. Le côté psychique doit probablement jouer ici un grand rôle.

Cela explique peut-être aussi, dans le cas où des pères de famille se trouvaient parmi les ouvriers travaillant par roulement, que l'on ait observé une amplification inégale de la sensibilité aux bruits d'enfants.

KNAUT (République fédérale d'Allemagne)

Sachant que les parents réagissent aux bruits de leurs propres enfants autrement qu'aux bruits d'autres enfants, nous n'avons choisi que des sujets qui n'étaient pas pères de famille.

ALTERATION IN URINARY D-GLUCARIC ACID EXCRETION AS AN INDICATION OF EXPOSITION TO XENOBIOTICS

W. R. F. NOTTEN AND P. TH. HENDERSON

Institute of Pharmacology, University of Nijmegen, Netherlands

ABSTRACT

Many compounds foreign to the organism, particularly those which due to their high lipophilicity tend to remain for a long time in the body, are capable of stimulating a number of enzymes in the liver. On the one hand this affects the enzymes involved in the conversion of lipophilic toxic substances into more hydrophilic, non-toxic products. On the other hand the metabolism of "normal" body constituents can also be influenced. This stimulation, as a rule, becomes manifest in an enhanced excretion of metabolites by the urine. A well-known example is the stimulation of the D-glucuronic acid pathway in the liver, which leads to an enhanced excretion of L-ascorbic acid (in mammals excepting primates and the guinea-pig) and D- glucaric acid.

In view of this, it can be questioned whether the measurement of an enhanced urinary D-glucaric acid - as a reflection of an altered liver metabolism - can serve as a reliable test for the effect of exposure to body-foreign compounds. Such a test might be especially important when exposure takes place chronically to known agents at subtoxic concentrations, for which specific test methods are absent or hard to perform, and in those cases where exposition occurs to a varied spectrum of unknown xenobiotics.

Preceding page blank

During the present study a number of xenobiotic compounds (some drugs, organic solvents, pesticides and other environmental pollutants) were screened for their capacity to enhance urinary D-glucaric acid excretion in the guinea-pig and rat. The experimental results support the usefulness of the D-glucaric acid test as a measure of general exposition.

As far as the mechanism of the stimulation is concerned, it appears that the increased synthesis of D-glucaric acid is directly related to an acceleration of the conversion of UDPglucose to UDPglucuronic acid.

The applicability of the D-glucaric acid test for man in the field of industrial and environmental hygiene, is discussed.

1. INTRODUCTION

In industrial and environmental hygiene it is of great importance to estimate exposition to toxic substances as early as possible and at concentrations which do not yet lead to intoxication phenomena. Periodical diagnosing of persons or animals for exposure to xenobiotics at subtoxic concentrations may serve a double purpose. On the one hand one can guard against unacceptable toxic damage by excluding from further exposition, on the other hand indications can be found in order to take adequate measures with respect to the sources of pollution.

As amatter of fact, when exposition to certain known agents is the case, as often occurs in industry, specific tests are relevant. However, if suitable specific test methods are lacking or hard to perform, and in those cases where exposition occurs to a broad spectrum of unknown chemicals, it would be of great value to have the disposal of one or more non-specific test methods.

1.1. The D-glucaric acid test

Evidence has accumulated regarding the ability of many compounds, particularly those which due to their high lipophilicity tend to remain for a long time in the body, to induce the activities of the various drug-metabolizing enzymes[1-3]. It appeared also that exposure to chemicals foreign to the organism often leads to a stimulation of the glucuronic acid pathway, in which by sequences of biochemical processes hexose is transformed via D-glucuronic acid to L-ascorbic acid, D-xylulose and D-glucaric acid (see figure 1). Already in 1940 Longenecker et al.[6] reported that various drugs administered to rats enhance the urinary L-ascorbic acid excretion. Further investigations extended this phenomenon to other compounds and up to now a stimulative influence is known of a large variety of xenobiotic agents[4,5,8-11]. From this the suggestion was made that an enhanced urinary excretion of L-ascorbic acid may be used as an indicator of drug-induced alterations in the activities of drug-metabolizing enzymes in animals[1,8]. It is of particular importance for men, who is unable like other primates and the guinea-pig to synthesize L-ascorbic acid, that the stimulative effect of drugs on the glucuronic acid pathway also results in an enhanced urinary excretion of D-glucaric acid[11-14].

It was the purpose of the present study to find out if an altered

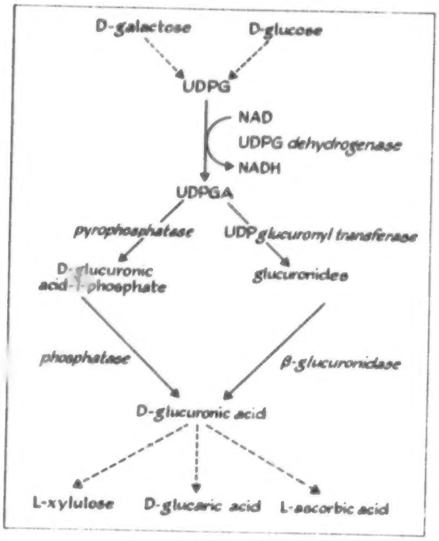

D-galactose
D-glucose
UDPG
NAD
UDPG dehydrogenase
NADH
UDPGA
pyrophosphatase
UDPglucuronyl transferase
D-glucuronic acid-1-phosphate
glucuronides
phosphatase
β-glucuronidase
D-glucuronic acid
L-xylulose
D-glucaric acid
L-ascorbic acid

Figure 1. The D-glucuronic acid pathway.

urinary D-glucaric acid excretion, in its turn, can be considered as an indication of previous intake of certain chemicals. In that case, the so-called D-glucaric acid test might be of value as a non-selective exposition test.

2. METHODS

2.1. Animals

Male Wistar rats (175-230 g) and male guinea-pigs (195-205 g) were utilized. All compounds were administered i.p. or p.o. (see tables). Control animals received saline or sesame oil in equivalent quantities.

For the measurements of the in vitro activities of the liver enzymes, the animals were killed by decapitation. The livers were rapidly removed and cooled in ice. Portions of liver were weighed, finely minced, and transferred into 4 vol. of ice-cold 0.25 M sucrose solution containing 5 x 10^{-2}M tris(hydroxymethyl)aminomethane-HCl (pH 7.4). Homogenates were prepared using a Teflon-glass homogenizer.

TABLE I. EFFECT OF CHRONIC TREATMENT WITH XENOBIOTICS ON IN VITRO ACTIVITIES OF HEPATIC N-DEMETHYLASE AND UDP-GLUCURONYLTRANSFERASE

compound	dose[+]	N-demethylation[‡] of aminopyrine		UDPglucuronidation[●] of p-nitrophenol	
		control	treated	control	treated
hexachloro-benzene	10	77 ± 9	77 ± 1	52 ± 3	64 ± 2^{xxx}
heptachlor	4	77 ± 9	81 ± 2	52 ± 3	46 ± 1
disulfiram	300	95 ± 6	143 ± 7^{xxxx}	58 ± 3	73 ± 1^{xxxx}
Perthane	100	90 ± 5	123 ± 2^{xxxx}	45 ± 2	46 ± 1
toluene	60	85 ± 8	108 ± 8	46 ± 4	44 ± 4
tetraethyl-lead	1.5	90 ± 5	105 ± 3^{x}	45 ± 2	46 ± 1
Aroclor 1260	1	108 ± 9	94 ± 5	49 ± 6	67 ± 3^{x}
ethanol	100	90 ± 5	111 ± 7^{x}	45 ± 2	54 ± 2^{xx}
n-hexane	3	108 ± 9	91 ± 4	49 ± 6	70 ± 4^{x}
Dodin	14	77 ± 9	37 ± 7^{xxx}	52 ± 3	44 ± 4
Atrazine	10	83 ± 4	86 ± 4	46 ± 5	41 ± 5
dimethoate	7	77 ± 9	55 ± 1^{x}	52 ± 3	47 ± 2
nitrobenzene	0.5	108 ± 9	107 ± 5	49 ± 6	77 ± 5^{xx}
aniline	1	85 ± 8	114 ± 4^{x}	46 ± 4	60 ± 5^{x}
benzene	1	108 ± 9	123 ± 7	49 ± 6	69 ± 5^{x}
phenylmercur-ic acetate	1.5	90 ± 5	95 ± 8	45 ± 2	26 ± 4^{xxx}

[+] in mg/kg/day; all compounds were administered i.p. in sesame oil, except for disulfiram, which was suspended in saline and given p.o. The duration of treatment is given in tableII.

[‡] Expressed as 10^{-8} moles formaldehyde produced per hour per mg of microsomal protein.

[●] Expressed as 10^{-7} moles p-nitrophenol conjugated per hour per mg of microsomal protein.

Values are means (± S.E.M.) of six animals.

xxxx: indicates significantly different from control at $P < 0.001$; xxx: idem at $0.001 < P < 0.01$; xx: $0.01 < P < 0.02$; x: $0.02 < P < 0.05$; for all further values $P > 0.05$ (Student's t-test).

Crude microsomal fractions were prepared from the homogenates by centrifugation at 9,000 g for 20 min at 2 °C.

2.2. Determination of D-glucaric acid in the urine

D-glucaric acid was estimated according to the method of Marsh[19] from the inhibitory effect of D-glucaro-1,4-lactone, to which it is converted by heating at pH 2, on β-glucuronidase.

Creatinine concentrations in the urine were estimated according to Gorther and de Graaff[20].

2.3. Enzyme assays

Microsomal N-demethylation of aminopyrine was measured in 9,000 g supernatants as described by Henderson and Kersten[21].

UDPglucuronyltransferase activities were determined in 9,000 g supernatants according to Henderson[22], except that for activation of the enzyme the supernatants were treated with the detergent Triton X-100 (0.25%, final conc.) instead of sonication. p-Nitrophenol was used as acceptor substrate.

2.4. Protein assay

Protein concentrations were determined following the method of Lowry et al.[23]. Bovine serum albumin (Sigma) was employed as reference standard.

3. RESULTS AND DISCUSSION

3.1. Comparison of the effects of chronic treatment with xenobiotics on drug metabolism and on urinary excretion of D-glucarate

It has been postulated by Hunter[12,15], Latham[24] and others that the urinary D-glucaric acid excretion might act as an indirect estimate of hepatic enzyme activity. In the present study, therefore, we tried to find out if alterations in enzyme activities involved in drug metabolism appear after treatment with various compounds, and whether such alterations are paralleled by similar changes in urinary D-glucarate levels.

Guinea-pigs were treated with relatively low doses of different xenobiotics, including some drugs, pesticides, hydrocarbons, for a few weeks. The effect on the in vitro activities of the oxidative N-demethylation of aminopyrine and the UDPglucuronidation of p-nitro-

TABLE II. EFFECT OF CHRONIC TREATMENT WITH XENOBIOTICS ON THE URINARY EXCRETION OF D-GLUCARIC ACID IN THE GUINEA-PIG

compound	dose[+]	D-glucaric acid[*] (microgram/24h)		per cent of control	treatment period (days)	
		control	treated		A	B
hexachlorobenzene	10	80 ± 6	372 ± 55^{xxx}	465	21	7
heptachlor	4	80 ± 6	301 ± 25^{xxx}	376	21	7
disulfiram	300	86 ± 3	166 ± 8^{xxx}	193	8	3
Perthane	100	76 ± 7	122 ± 12^{xx}	157	21	14
toluene	60	72 ± 7	96 ± 4^{x}	133	21	21
tetraethyllead	1.5	76 ± 7	103 ± 7^{x}	132	21	21
Aroclor 1260	1	74 ± 5	98 ± 6^{x}	132	35	35
ethanol	100	76 ± 7	101 ± 6^{x}	129	21	14
n-hexane	3	74 ± 5	95 ± 4^{x}	128	35	35
Dodin	14	80 ± 6	103 ± 7^{x}	128	21	21
Atrazine	10	79 ± 6	94 ± 2^{x}	119	21	21
dimethoate	7	80 ± 6	94 ± 11	118	21	-
nitrobenzene	0.5	74 ± 5	86 ± 8	116	35	-
aniline	1	74 ± 5	82 ± 8	111	35	-
benzene	1	74 ± 5	78 ± 9	105	35	-
phenylmercuric acetate	1.5	76 ± 7	46 ± 10^{x}	51	21	14

[+] in mg/kg/day; all compounds were administered i.p. in sesame oil, except for disulfiram, which was suspended in saline and given p.o.

[*] Expressed as microgram/24 h/100 gram body weight; values are means (± S.E.M.) of six animals.

B: indicates the day at which the first significant ($P < 0.05$) alteration in the urinary excretion of D-glucaric acid was observed.

A: indicates the total duration of the treatment. The D-glucaric acid levels mentioned were measured during the last 24 h of this period.

xxx: means significantly different from control at $P < 0.001$; xx: idem, at $0.01 < P < 0.02$; x: $0.02 < P < 0.05$. For all further values $P > 0.05$ (Student's t-test).

TABLE III. EFFECT OF SHORT-TERM TREATMENT WITH RELATIVELY HIGH DOSES OF SOME XENOBIOTIC AGENTS ON THE URINARY EXCRETION OF D-GLUCARIC ACID

compound[+]	D-glucaric acid[++]		per cent of control	treatment period (h)
	control	treated		
barbital sodium	104 ± 8	330 ± 36^{xxx}	317	8
phenobarbital	104 ± 8	224 ± 24^{xxx}	215	8
nikethamide	104 ± 8	272 ± 36^{xx}	261	8
chlorbutol	95 ± 8	135 ± 14^{x}	142	8
DDT	95 ± 8	188 ± 20^{xx}	198	8
Perthane	151 ± 14	423 ± 49^{xxx}	324	24

[+] barbital sodium (150 mg/kg, i.p.), phenobarbital (130 mg/kg, i.p.), nikethamide (130 mg/kg, i.p.), chlorbutol (150 mg/kg, p.o.), and DDT (60 mg/kg, p.o.) dissolved in saline were administered to male Wistar rats (175-230 g) in two doses, at zero time and at 4 h. Controls received an equivalent volume of saline. Perthane dissolved in sesame oil was administered i.p. (500 mg/kg) to male guinea-pigs (195-205 g); control animals received an equivalent volume of sesame oil.

[++] Amount of D-glucaric acid present in the urine collected during the whole period. Values represent means (± S.E.M.) of six animals.

xxx: significantly different from the control at $P < 0.001$; xx: at $0.001 < P < 0.01$; x: at $0.02 < P < 0.05$ (Student's t-test).

phenol (two typical examples of drug-metabolizing reactions) is demonstrated in table I. Only disulfiram, ethanol and aniline treatment led to an enhanced rate of N-demethylation and glucuronidation. Perthane, tetraethyllead, Dodin and dimethoate increased only the N-demethylating activity, whereas hexachlorobenzene, Aroclor 1260, n-hexane, nitrobenzene, and benzene enhanced only the activity of UDPglucuronyltransferase. In contrast, the glucuronidating activity was found to be reduced after treatment with phenylmercuric acetate. Heptachlor, toluene and Atrazine exhibited no influence on the in vitro activities of these drug-metabolizing enzymes. From these results it can be concluded that with regard to drug metabolism several of the compounds can act as specific inducers.

As is seen in table II, treatment of the guinea-pigs with most of the chemicals under investigation led to a significantly enhanced excretion of D-glucaric acid. Only dimethoate, nitrobenzene, aniline, and benzene did not exhibit a measurable influence, whereas phenylmercuric acetate markedly inhibited the urinary D-glucaric acid excretion.

Obviously, induction of the drug-metabolizing system is not always accompanied by an enhancement of the urinary D-glucarate excretion, as is demonstrated by the action of dimethoate, nitrobenzene, aniline and benzene. On the other hand, heptachlor, toluene and Atrazine stimulated the glucuronic acid pathway, but left the drug-metabolizing enzymes unaffected.

3.2. Effect of short-term treatment on the D-glucaric acid excretion

The conclusion that stimulation of the D-glucuronate pathway, leading to an enhanced D-glucaric acid excretion, is not necessarily related to an induction of the drug-metabolizing enzymes is further supported by the results from some short-term experiments.
Rats were treated for 8 hours with relatively high doses of barbital, phenobarbital, nikethamide, chlorbutol, or DDT. Guinea-pigs were treated with Perthane for 24 hours, as indicated in table III.

No alteration in N-demethylase and UDPglucuronyltransferase activities could be observed at the end of the treatment period. However as appears from the data given in table III, all compounds caused a significant enhancement of the D-glucaric acid excretion within 8, or 24 hours, respectively.

Further experiments pointed out that stimulation of the D-glucuronate pathway presumably is based on an accelerated synthesis of UDPGA. It appeared also that, at least in cases of short-term treatment, this stimulation is independent of a drug-induced de novo synthesis of UDPGdehydrogenase, the enzyme which catalyzes the conversion of UDPG into UDPGA[17].

3.3. Normal values of the urinary D-glucaric acid excretion in man

On account of the results obtained from the animal experiments as mentioned above, the D-glucaric acid excretion can be used as an index of hepatic enzyme induction only in some particular cases. But, as it appeared that, irrespective of an enzyme induction, in the majority of cases treatment with xenobiotics caused a clear alterat-

TABLE IV. NORMAL VALUES OF URINARY D-GLUCARIC ACID EXCRETION IN MAN

urine	µg D-glucaric acid/mg creatinine		
	mean	inner limits for $P_{2.5}$ - $P_{97.5}$	outer limits for $P_{2.5}$ - $P_{97.5}$
collected for 24 h (A)	9.9	5.4 - 15.5	3.7 - 17.2
collected overnight (B)	9.8	5.2 - 15.3	3.4 - 16.0
A minus B	10.3	4.3 - 17.6	2.5 - 20.7

urine	µg D-glucaric acid/hour		
	mean	inner limits for $P_{2.5}$ - $P_{97.5}$	outer limits for $P_{2.5}$ - $P_{97.5}$
collected for 24 h (A′)	635	349 - 999	219 - 1373
collected overnight (B′)	603	260 - 1150	177 - 1253
A′minus B′	663	307 - 1083	191 - 1437

The confidence intervals for the percentiles $P_{2.5}$ and $P_{97.5}$ are constituted with $\gamma = 90\%$. The number of samples was 110.

ion in the D-glucaric acid level, the usefulness of the D-glucaric acid excretion as a non-selective exposition test has to be seriously considered. This prompted us to extend our studies to the D-glucaric acid excretion by the urine in man.

Normal values were determined according to the procedure described by Rümke and Bezemer[18]. In this method for statistical analysis of normal values two types of tolerance limits are distinguished. The inner limits for percentiles are recommended as warning limits, the outer limits as limits for more descriptive purposes.

With respect to the general applicability of the D-glucaric acid test collecting of urine for 24 hours may encounter some practical

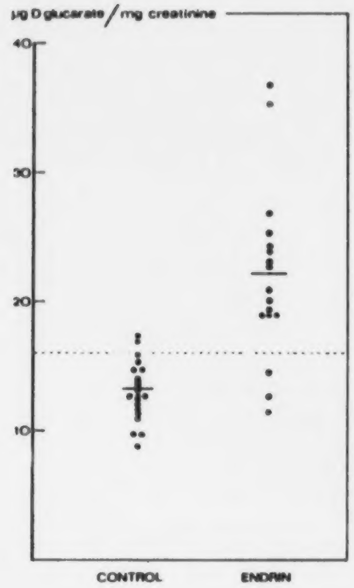


Fig. 2. Comparison of the D-glucaric acid excretions of some industrial workers exposed to endrin with those of some office workers. The broken horizontal line indicates the upper limit of the normal values (Table III). Note: nearly all values of the Endrin group are beyond this limit.

difficulties. Therefore, normal values of D-glucaric acid related to the urinary creatinine concentration, have been compared with the D-glucaric acid excretion per hour, both for 24 hours urine collections and urine samples collected overnight. 110 Young healthy human subjects were tested in this study. The results are presented in table IV. No substantial fluctuations in the daily D-glucaric acid occur. Further, it can be derived that reliable values of the D-glucaric acid excretion can be obtained if expressed per mg creatinine. Further investigations, in which persons working in different branches of chemical industry are tested for their urinary excretion of D-glucaric acid, in order to assess the validity of the test in industrial and environmental hygiene, are in progress now. (Fig. 2)

Acknowledgement

This work was supported by a grant from the Prevention Fund of the Dutch Ministry of Health and Environmental Hygiene.

REFERENCES

1 CONNEY, A.H.,"Pharmacological implications of microsomal enzyme induction", Pharmacol. Rev., 19, 317 (1967).

2 ZEIDENBERG, P., ORRENIUS, S, ERNSTER, L., J. Cell Biol., 32, 528 (1967).

3 MULDER, G.J., Biochem. J., 117, 319 (1970).

4 BURNS, J.J., EVANS, C., J.Biol. Chem., 223, 897 (1956).

5 BURNS, J.J., EVANS, C., TROUSOF, N., J. Biol. Chem., 227, 785 (1957).

6 LONGENECKER, H.E., FRICKE, H.H., KING, C.G., J. Biol. Chem., 135, 497 (1940).

7 CONNEY, A.H., BURNS, J.J., Nature, 184, 363 (1959).

8 AARTS, E.M., Biochem. Pharmacol., 17, 327 (1968).

9 CONNEY, A.H., BRAY, G.A., EVANS, C., BURNS, J.J., Ann. N.Y. Acad. Sci., 92, 115 (1961).

10 CONNEY, A.H., GILLETTE, J.R., INSCOE, J.K., TRAMS, E.R., POSNER, H.S., Science, 130, 1478 (1959).

11 MARSH, C.A., REID, L.M., Biochim. Biophys. Acta, 78, 726 (1963).

12 HUNTER, J., CARELLA, M., MAXWELL, J.D., STEWART, D.A., WILLIAMS, R., Lancet I, 572 (1971).

13 OKADA, M., MATSUI, M., KAISU, T., ABE, F., Chem. Pharmac. Bull., 17, 2625 (1969).

14 HUNTER, J., MAXWELL, J.D., STEWART, D.A., WILLIAMS, R., Nature, 237, 399 (1972).

15 HUNTER, J., MAXWELL, J.D., STEWART, D.A., WILLIAMS, R., Biochem. Pharmacol., 22, 743 (1973).

16 AARTS, E.M., Biochem. Pharmacol., 14, 359 (1965).

17 NOTTEN, W.R.F., HENDERSON, P.Th., submitted for publication.

18 RUMKE, Chr.L., BEZEMER, P.D., Ned. T. Geneesk., 116, nr. 35, 1559 (1972).

19 MARSH, C.A., Biochem. J., 87, 82 (1963).

20 GORTHER, E., de GRAAFF, W.C., Klinische Diagnostiek, 7e druk, p. 440, Stenfert Kroese N.V., Leiden (1955).

21 HENDERSON, P.Th., KERSTEN, K.J., Biochem. Pharmacol., 19, 2343 (1970).

22 HENDERSON, P.Th., Life Sciences, Part II, 9, 511 (1970).

23 LOWRY, O.H., ROSEBROUGH, N.J., FARR, A.L., RANDALL, R.J., J. Biol. Chem., 193, 265 (1951).

24 LATHAM, A.N., J. Pharm. Pharmac., 26, 285 (1974).

DISCUSSION

de BRUIN (Netherlands)

1. In connection with the observation that several non-enzyme inducing agents also cause anoumalous excretions, which mechanisms could be responsible for the augmented elimination of L-glucaric acid, apart from microsomal enzyme induction?

2. Is there any evidence that compounds which inhibit drug metabolizing enzyme systems, either directly or by way of hepatotoxic damage, might have a lowering effect upon L-glucaric acid output?

3. Can the sensitivity of the glucaric acid test be indicated, especially as compared to similar enzyme-inductive tests, such as alteration of drug disposition or change in endogenous steroid hydroxylation?

NOTTEN (Netherlands)

1. As mentioned already the stimulation of the glucuronate pathway presumably is based upon an enhanced synthesis of UDPGA from UDPG. In case of chronic treatment this may be due to an increased synthesis of the non-microsomal enzyme UDPG-dehydrogenase. From our short-term experiments it appeared that urinary glucaric acid has been elevated even within 8 hours. This indicates that another mechanism is involved. One can imagine, that in this case, the conversion of UDPG into UDPGA can be accelerated as a consequence of altered enzyme biometrics. On the other hand, since it was found in some preliminary studies that an enhanced

synthesis of D-glucaric acid is accompanied by an inhibition of the glycogen synthesis, the possibility exists that more UDPG becomes available as substrate for the glucuronate pathway.

So, it is likely that stimulation of the D-glucuronate pathway and induction of microsomal drug metabolism are regulated by different mechanisms.

2. Yes, phenylmercuric acetate lowers the glucuroxidation rate (table I) and at the same time already inhibits the D-glucaric acid synthesis (table II). The same phenomenon has been observed with disulfriam after a 24-hour treatment.

3. As far as the sensitivity in comparison with other tests is concerned, no studies have been done.

The D-glucaric acid test, however, is preferable to the tests mentioned by you, because analysis of D-glucaric acid is rapid and easy to perform. This in contrast to a determination for example 6 -β- hydroxy steroids (enzyme induction test). On the other hand, in the D-glucaric acid test no drugs have to be administered to the persons being tested, as is the case of a drug disposition test (antipyrine). Hence, the D-glucaric acid test is more suitable as a general test.

ZIELHUIS (Netherlands)

1. How long does increased glucaric acid excretion persist after exposure? In the Netherlands Jager found increased excretion in ex-endrin workers. Endrin has a very short biological half life. Could you explain that?

2. In our experience the intra-individual coefficient of variation of ALA-excretion if measured per gram of creatinine is about similar as if measured per hour in case of overnight urine. What is your opinion on the comparative coefficients of variation of both methods? In my opinion it is certainly possible in occupational health studies to apply the time-correction method; it only demands some extra organisation and it does not load the laboratory with creatine measurement.

NOTTEN (Netherlands)

1. We have not measured how long the increase of D-glucaric acid excretion lasts after stopping the treatment. Therefore, we cannot explain this.

2. We also found comparable variation coefficients of D-glucaric acid excretion both if related to the urinary creatinine concentration and if expressed per hour. The only reason for expressing urinary D-glucaric acid per mg creatinine, is a practical one. We prefer the very simple routine-assay of creatinine to the extra risks of making mistakes in a more complex sampling scheme of urines.

THE ASSESSMENT OF ENVIRONMENTAL CARCINOGEN RISKS IN TERMS OF LIFE SHORTENING

ROY E. ALBERT AND BERNARD ALTSHULER

Institute of Environmental Medicine, New York University Medical Center, NY, USA

ABSTRACT

This paper presents an approach to the assessment of carcinogen risks in which the dominant effect of carcinogen exposure is life shortening and the impact falls both on those individuals who would have got cancer without the carcinogen exposure as well as the new cancer cases. This analysis is based on the interaction of age-specific tumor incidence rates and population survival in terms of age-specific mortality rates without the induced risk from carcinogen exposure; the analysis yields estimates for life-time probability of developing cancer, average life-span lost by the entire population, the average age of cancer occurrence and the average life-span loss of cancer cases. The approach utilizes the animal response data to assign, to the existing human cancer occurrence, an equivalent dose of the same carcinogen which is under consideration in terms of risk evaluation. The approach has the advantages of (a) keying the estimates of carcinogen risks to those which already exist in the environment, (b) avoiding large extrapolations from animal data, and (c) encompassing the variability in susceptibility and carcinogen exposure in humans.

Carcinogens can pollute the environment from technological processes that are too important to abandon, as for example, the combustion of fossil and nuclear fuels for production of electricity. Hence, it is necessary to estimate the magnitude of cancer risks from environmental contamination as an essential part of the process of weighing the costs of controlling the release of carcinogens against the consequences of deleterious health effects and thus to make a rational choice between alternative technological processes that achieve the same ends.

The assessment of cancer risks from exposure to known environmental carcinogens is an exceedingly difficult problem. Carcinogen exposures will never be tolerated unless they are expected to cause negligible increases in the existing burden of cancer; unless there is a grave miscalculation in the formulation of exposure limits, the actual risks could never be feasibly measured in human and certainly not in experimental animals. There are additional uncertainties associated with differential sensitivity amongst humans and between humans and test animals.

In principle, the only feasible basis for risk extrapolations to very low levels of carcinogen exposure is to develop a sound understanding in animals of the component processes that determine the dynamics of tumor formation and thereby establish the general principles for making risk extrapolations. It is also necessary to use epidemiologic data on human cancer in response to define levels of exposure in order to equate the relative sensitivities of human and animal for particular target organs and carcinogens. The conventional method of assessing carcinogen hazards is done by relating the level of dose to cancer incidence. This implies that the extra cancer cases bear the full effect of the carcinogen exposure and the rest of the population suffers no ill effects. No attention is paid to the age at which new cancer cases occur or to the possibility that additional carcinogen exposure could affect individuals who were going to get cancer from other causes. The shape of the dose-incidence curve used for extrapolations is arbitrary as for example in the case of the Mantel-Bryan approach which uses a log-normal dose-response curve with a slope of one probit per log dose (1). The thrust of this paper is that the temporal patterns of mortality-corrected tumor incidence should be used as the primary basis for characterizing tumor responses from chronic carcinogen exposure since they are more directly related to the time-dependent processes of neoplastic cell transformation and growth of transformed cells into tumors; the incidence and age of at which tumors form depend on the interaction of the temporal tumor response patterns with population survival. This approach provides a more complete characterization of carcinogen risks since the effects are defined not only in terms of the excess cancer incidence but also in terms of life shortening. Furthermore, the approach provides a way to link the responses observed in test animals to that already occurring in the same target organ in humans and to circumvent the need for very large extrapolations.

Strong evidence exists for a simple and systematic relationship between the magnitude of chronic life-time carcinogen exposure and the temporal behavior of tumor incidence when corrected for intercurrent mortality by conventional life-table techniques. The early work by Blum on the induction of skin cancer in the mouse by ultraviolet radiation (2) and the later studies of Druckrey with various chemical carcinogens on a variety of target organs (3) gave a mathematical formulation to the common experience that the higher the level of carcinogen exposure the earlier the appearance of tumors. These investigators showed that at a given dose level, the cumulative incidence of tumors can be represented by a log-normal distribution of time to tumor occurrence. Thus, the overall response can be expressed in terms of the median time, t, for tumor formation. The geometric standard deviation, σ_g, of the cumulative incidence provides a measure of the temporal dispersion of the individual response times, i.e., the larger the geometric standard deviation the more heterogenous the response.

The relationship between the daily dose of carcinogen, d, and the median time of tumor induction t was $dt^n = c$ where n and c are constants for a particular carcinogen and test system and the standard deviation σ_g was insensitive to dose rate. As shown elsewhere, the interaction of the log-normal tumor incidence curve with the population survival curve yields the cancer incidence, the average age at which cancer develops, and the average amount of life lost by the individuals developing cancer and the amount of life lost averaged over the whole population; the values of n and σ_g have important effects on the dose-response relationships (4).

The above formulation implies that a given dose level of carcinogen, every exposed individual would develop cancer if he lived long enough. The individuals that actually develop tumors are the more susceptible members of the exposed population; those that do not develop cancer are simply less susceptible and die from extraneous causes before they have a chance to develop cancer. The contrast between the effects of higher and lower carcinogen exposure levels is that the time of tumor occurrence is shortened by the higher dose level in all exposed individuals by the same proportion. Thus, the susceptibles develop cancers earlier than at the lower exposure and the additional cancer cases occur because they now die before other causes instead of afterward (in principle).

The applicability of $dt^n = c$ formulation to human cancer is illustrated by the comparison of stomach cancer in USA, Germany and Japan (5, 6). In all three areas, the cumulative mortality-corrected incidence is log-normal with the same σ_g of 1.5. It is a reasonable supposition that dietary factors are responsible for the differences in cancer experiences in the three countries. The parallel log-normal cumulative incidence curves supports the notion that incremental carcinogen exposure shortens cancer development by a constant factor in the entire population. On the assumption that $n = 2$, the equivalent carcinogen exposure is thirty percent higher in Germany and twice as high in Japan relative to New York State. The large value of the geometric standard deviation for stomach cancer in all three countries (σ_g = 1.5) suggests the existence of a considerable heterogeneity in the combined effects of susceptibility and carcinogen dose.

The epidemiological data on stomach cancer illustrates the generally accepted notion that much of the current cancer experience in humans is due to exposure to environmental carcinogens. It follows that the impact of additional carcinogen exposure should be described in terms of its interaction with the existing cancer experience and presumed carcinogen exposure. The biggest impact that a small additional carcinogen exposure could have on a population (that is already substantially exposed to carcinogens) would occur when the additional and existing carcinogens were the same agents. This would shift the entire log-normal response curve to an earlier age. By contrast, if the actions were entirely independent, the small additional carcinogen exposure would have its own log-normal incidence curve occurring at a later time than that of the existing carcinogen exposure. The summated effects of the two log-normal curves would result in a deformed log-normal curve with tumor development foreshortened only at the more advanced ages.

A simple and conservative approach for estimating cancer risks could involve the use of the tumor response data in test animals (for the particular carcinogen whose risk is under consideration) to assign an equivalent carcinogen dose, d_o, to the existing cancer experience in the human population to be exposed. The d_o dose is thus one that produces in animals a comparable temporal response to that currently experienced by humans when the two species are normalized for differences in life-span and under the assumption of equal average susceptibility in humans and the test animals. The impact of an additional carcinogen dose, d, is evaluated in humans in terms of the $d_o + dt^n = c$ formulation.

To illustrate the application of animal data to the assignment of an equivalent carcinogen dose d_o to human cancer and the subsequent estimation of risks, let us suppose that we are concerned about the risks from the carcinogen diethylnitrosamine (DENA) which is assumed to

Table I Effect on various response parameters of the indicated percentage increments in equivalent carcinogen dose for liver cancer occurrence in Connecticut males, 1962-64.

Percent Increment in Equivalent Carcinogen Dose for Current Liver Cancer Experience	t	$p \times 10^{-4}$	$\bar{x}$	$\Delta \times 10^{-2}$	δ
0	350	18.9	71.27	2.12	11.21
2	347	20.0	71.20	2.25	11.24
5	342	21.7	71.07	2.51	11.32
10	334	24.6	70.87	2.92	11.43

t = median age of cancer occurrence (years)

p = probability of cancer

$\bar{x}$ = average age of cancer occurrence (years)

Δ = average life-span loss in entire population (years)

δ = average life-span loss of cancer cases (years)

Table II The effect of 0.2 μg/kg/day of DENA on the incidence, average age of tumor occurrence and life-span loss of spontaneous and new hepatic cancer cases.

	Incidence per 10^4	Average Age (years)	Life-Span Loss (years)
"Spontaneous" Cases (no DENA)	18.9	71.27	----
"Spontaneous" Cases (with DENA)	18.9	67.85	3.42
Extra Cases	5.7	80.75	1.99
Total Cases	24.6	70.87	----

produce only primary liver cancer in humans. A log-normal temporal response for liver tumors over a wide range of dose rates of DENA with an n equal to 2.2 has been reported by Druckrey for an inbred strain of rats (3). The cumulative incidence of primary liver cancer reported by the Connecticut State Tumor Registry for males in 1962-1964 (6) is log-normal with a σ_g of 1.7 and an extrapolated median time, t, of 350 years. For purposes of illustration, it is assumed that one year of human life-span is equal to 1.52 weeks of life-span in rats. The median time t of 350 years corresponds to 535 weeks in rats. The plot of log d vs log t for the DENA response of rats is linear and extrapolates to a dose of about 2 μg/kg/day at 535 weeks which is taken to be the equivalent dose d_o for the background primary liver cancer experience in men. Computer calculations have been done for normalized tumor responses covering a range of values of n and σ_g to obtain values for incidence, average age at cancer occurrence and the average amount of life-span lost by cancer cases (4). In these calculations, d was normalized to unity for t equal to the 62 year mean life-span of humans. It is assumed that humans exposed to DENA will show the same n value as that observed in rats, i.e., n = 2.2, but σ_g which is a measure of heterogeneity of response, is taken to be that for the observed primary liver cancer occurrence in humans, namely, σ_g = 1.7. Table I presents, for various percent increments in the DENA equivalent dose d_o for background liver cancer occurrence, the calculated values of t (median age), p (life-time probability of developing cancer), Δ (average life-span lost by the entire population), $\bar{x}$ (the average age of cancer occurrence) and δ (the average life-span loss of cancer cases).

To understand the significance of these figures let us examine, for example, the effects of the 10% increase in the equivalent carcinogen dose, i.e., 0.2 μg/kg/day. This carcinogen exposure reduces the time of tumor occurrence by 4.8%. The effects in the average age of cancer occurrence and the corresponding losses in life-span are tabulated in Table II. The average age of the $18.9/10^4$ cases which occur at background exposure will be reduced by 4.8% from 71.27 years to 67.85 years. These spontaneous cancer cases would therefore lose 3.42 years of life due to the carcinogen exposure. Furthermore, the incidence rises from $18.9/10^4$ to $24.6/10^4$ with the carcinogen exposure so that there are an extra $5.7/10^4$ cancer cases. However, the average age of cancer development for all the cancer cases which occur in association with the carcinogen exposure ($24.6/10^4$) decreases only slightly from 71.23 years at background exposure to 70.87 years with the carcinogen exposure. Since the carcinogen exposure reduces the average age of the original $18.9/10^4$ cancer cases to 67.89 years, the $5.7/10^4$ extra cancer cases must have developed at an average age of 80.75 years since the overall average age of cancer development in association with the carcinogen exposure is

70.87 years.

As a result of the carcinogen exposure and the consequent foreshortening of the cancer time, the extra cancer cases die somewhat before other causes of death instead of somewhat later (in principle) so that the actual life shortening is roughly one-half the full 4.8% life-span loss of the original cancer cases. Hence, the average age of death at 80.75 years represents a 2.4% reduction from what it would have been without the carcinogen exposure, i.e., 82.74 years and, consequently, the extra cancer cases suffer a 1.99 year loss of life due to the carcinogen exposure. This is substantially less than the 3.42 years lost by the original cancer cases and it also occurs later in life so that the major brunt of the life shortening is born by those cancer cases who would have gotten their disease without the additional carcinogen exposure.

References

1. MANTEL, N., BRYAN, W.R., "Safety" testing of carcinogenic agents, J. Nat. Cancer Inst., 27, 455-470 (1961).

2. BLUM, H. F., Carcinogenesis by ultraviolet light, Princeton University Press, Princeton, New Jersey, 1959.

3. DRUCKREY, H., "Quantitative aspects of chemical carcinogenesis", Potential carcinogenic hazards from drugs, evaluation of risks, UICC Monograph Series, Vol. 7, pp. 60-78, (Rene Truhaut, Ed.), Springer-Verlag, New York, 1967.

4. ALBERT, R. E., ALTSHULER, B., "Considerations relating to the formulation of limits for unavoidable population exposures to environmental carcinogens", Radionuclide carcinogenesis, (C. L. Sanders, R. H. Busch, J. E. Ballou and D. D. Mahlum, Eds.), AEC Symposium Series, CONF-720505, NTIS, Springfield, Virginia, June, 1973, pp. 233-253.

5. Cancer incidence in five continents, Vol. II, (R. Doll, C. Muir and J. Waterhouse, Eds.), (Geneve, International Union Against Cancer, 1970), Distributor: Springer-Verlag, Berlin, Heidelberg, New York.

6. Cancer incidence in five continents. A technical report. (R. Doll, P. Payne and J. Waterhouse, Eds.), (Geneve, International Union Against Cancer, 1966), Distributor: Springer-Verlag, Berlin, Heidelberg, New York.

DISCUSSION

CROCKER (U.S.A.)

Do you have data for life shortening in animals that do not develop tumors? The reason for this question is that life shortening as such may be an important concomitant of exposure to carcinogens. Premature aging and life shortening are associated with chronic, low-grade X-ray exposure and in turn with increased lesions (renal glomerular sclerosis, for example) commonly recognized as age-related. X-irradiation is also "carcinogenic" though doses used for demonstrating this property are usually high. It would therefore seem particularly useful to include calculation of non-specific life-shortening in animals experiments in which the exposure regimen has produced tumors in some animals but not in all animals under exposure.

ALBERT (U.S.A.)

The point is well taken, but so far we have not looked at the temporal aspects of the dose-response relationships for non-specific life-span shortening to examine the similarities and differences with respect to tumor formation.

MAGE (Denmark)

Any data can be plotted on log probability paper, and scatter will exist. If one makes the assumption that these data are random samples from a log-normal distribution then the line must pass through the geometric mean of the data at 50%

$$\mu = \frac{\sum_{i=1}^{n} \log X_i}{n},$$

with Xgm = $e/^{u}$.

The 50% occurrence must be plotted at a value Xg.m = $e/^{u}$. The slope of the line is determined from the standard geometric deviation of the data.

In your equation was your "median" value determined in this manner? If not, on what statistical basis can you justify, or better, with what confidence level can you state that the distribution is lognormal?

ALBERT (U.S.A.)

Whether the cumulative incidence of tumors at a given dose level is truly log-normal is an important question. considering the uncertainties in the temporal response data from most experiments and the general lack of data below the 5% response level, we have examined the matter only to the extent of satisfying ourselves by an eye fit that such data as we have looked at, is consistent with the log-normal pattern.

ERFORDERNISSE IM HINBLICK AUF MESSUNGEN
MONITORING NEEDS
BESOINS EN MATIERE DE MESURE DE L'EXPOSITION
NECESSITA' RELATIVE ALLA MISURA DELL'ESPOSIZIONE
EISEN VOOR HET TOT STAND BRENGEN VAN TOEZICHT OP EXPOSIE

Panel

Vorsitzender - Chairman - Président - Presidente - Voorzitter

T. SCHNEIDER (Nederland)

Preceding page blank

POLLUTANT-ORIENTED INTEGRATED MONITORING SYSTEMS AND LEAD EXPOSURE ASSESSMENT

E. A. SCHUCK, G. B. MORGAN, D. S. BARTH

Environmental Protection Agency, National Environmental Research Center, Las Vegas, Nevada, USA

ABSTRACT

A recent USEPA sponsored workshop panel of medical and monitoring experts concluded that the quantities of lead emitted into the environment have significantly degraded the quality of man's food, water and air supplies - as well as contaminating all exposed surfaces - and that motor vehicles using leaded gasolines contribute about 90% of these airborne and settled lead particles.

Evidence indicates that blood-lead concentrations increase with proximity to central urban areas and heavy traffic. Young children, particularly in central urban areas, are more susceptible to lead poisoning, absorb more lead, and may have a higher body burden (5 to 10 times more) on a body weight basis than do adults.

Little precise information is known concerning the subclinical pathological effects of lead poisoning. The destruction or partial incapacitation of the brain and other nerve tissues are of particular concern. Furthermore, permanent neural and organ damage may occur prior to birth, for lead has long been associated with aborted fetuses and stillborns. On the basis of public health surveys, it has been estimated that between 5,000 and 25,000 children per year suffer adverse effects from lead in the United States with known deaths at a rate of about 200 per year.

In conclusion, the panel strongly recommended that an intensive research monitoring system be designed and implemented to quantitate the exposure and effects of chronic environmental lead exposures to man.

1. Introduction.

Medical and environmental monitoring experts were convened by the National Environmental Research Center-Las Vegas (NERC-LV) in March 1974 to discuss and assess the present state-of-knowledge about lead--its sources, exposure pathways, and physiological and environmental effects--for the purpose of developing concepts necessary for determining the feasibility of establishing an integrated environmental research monitoring system and its requirements.

A practical and effective integrated research monitoring system is needed to complement basic research in determining the physiological and environmental effects of numerous pollutants, to identify and map areas of concern, to provide reliable trend data, and to establish realistic control measures.

The need for environmental research monitoring results from recognition that man and his activities have a substantial modifying effect on the environment. Assuming the existence of a well-planned research monitoring program suggests an ability to prevent the occurrence of detrimental or undesirable environmental effects. To date, however, most research monitoring programs have developed for reasons other than prevention. Thus, research monitoring programs are instigated only after environmental pollution has resulted in substantial detrimental and undesirable effects.

In such a situation, the demand for information becomes intense concerning the nature of the problem--the causes, the consequences, and the solutions. The resulting research monitoring program cannot meet these demands within the short time frame required. Consequently, such programs contain very little planning and tend to focus on those aspects assumed to be most important. Solutions, therefore, are frequently based on a grossly inadequate data base--inadequate to the point of leading to control actions which have dubious value and which are executed at great costs in resources. This situation cannot be permitted to continue and leads to the necessity for adequate planning and execution of environmental research monitoring activities.

Recognition of this need has resulted in the assignment of resources at NERC-LV to investigate the design of a pollutant-oriented integrated monitoring system. Such a system would take into account sources, transport, interactions, exposure, and dose in all applicable media. Also involved are sampling site selection, methods, and analysis, data collection and presentation, and quality assurance for the system and its individual components.

In recent decades, there has been a tremendous increase in both the number and concentrations of man-produced substances entering the environment. The effects of these substances at various exposure and dose levels and rates is often unknown or is only poorly defined. While any one of these substances may be harmless in itself, it may become harmful in combination with other materials or under certain environmental conditions. For instance, one effect which is inadequately known that could lead to widespread detrimental consequences to man is the potentiating effect which one substance might induce in others. The present state-of-knowledge about these substances and their effects and interrelationships is inadequate. The known harmful effects, and the large number of potentially harmful effects not presently known, necessitate the establishment of some form of integrated monitoring system to map, study, and aid in controlling these substances. Many scientific research projects are also needed.

In order to develop a practical and effective monitoring approach, this workshop was held to develop concepts and to determine the feasibility of such a system using lead as a test case. Lead was selected because of the copious amount of data available on it, because it presents a worldwide problem, and because it enters man and his environment in many forms and by various media. Consequently, research monitoring concepts developed for lead should also apply to many other environmental pollutants.

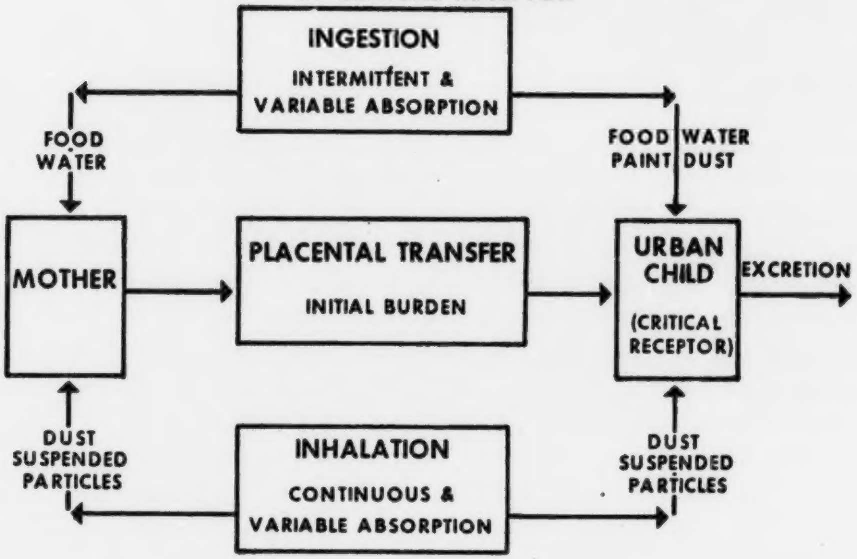
2. Discussion.

Lead, which is found in the earth's crust, also occurs naturally in the atmosphere and hydrosphere as a result of both physical and chemical processes. Man's activities, of course, introduced the greatest quantities of lead and lead compounds into the atmosphere and hydrosphere. For example, lead or its compounds can enter the environment at any stage during the mining, smelting, processing, and use of this metal and its derivatives. Additionally, lead is stable and incrementally accumulates as a waste or contaminant.

Increases in lead use have been on the order of 3% per year over the last decade, and the total annual consumption of lead in the United States is approximately 1.5 million short tons. Fortunately, most of this lead is not in a form or use likely to pose an environmental or health threat.

Major sources of lead causing or likely to cause adverse environmental or health effects include exhaust from the use of leaded gasoline (this contribution alone accounts for about 90% of the airborne and settled lead particles) and some other common fuels such as coal; the use of paint, ink, coloring, and other pigments containing lead; the use of lead in treating, processing, and packaging food; the use of lead in water pipes and pesticides; the use of lead as a stabilizer in the manufacture of certain plastics; the use of lead in candle wicks; and the mining, smelting, processing, and terminal disposal of lead containing materials. These and other sources bring large quantities of lead into man and his environment via the air, water, and food cycles. Figure 1 portrays the major pathways to a critical receptor.

During the past few years, environmental lead has been the subject of several publications and reviews. Based on these efforts, the population at risk, i.e., the critical



MAJOR PATHWAYS AFFECTING LEAD BURDEN IN CRITICAL RECEPTOR

INGESTION
INTERMITTENT & VARIABLE ABSORPTION
FOOD
WATER
FOOD
WATER
PAINT
DUST
MOTHER
PLACENTAL TRANSFER
INITIAL BURDEN
URBAN CHILD
(CRITICAL RECEPTOR)
EXCRETION
DUST
SUSPENDED PARTICLES
INHALATION
CONTINUOUS & VARIABLE ABSORPTION
DUST
SUSPENDED PARTICLES

FIGURE I.

receptor, in the United States has been identified as the urban child of one to three years of age. However, neurological damage may have actually occurred at an earlier period with the effects first appearing at a later stage of development. In addition, these effects may be too subtle to be easily recognized since they may gradually progress with growth and maturation. An example of the acute effects of high blood-lead concentrations in a pregnant mother and her newborn infant are well illustrated in a case reported by Palmisano et al. [1] in which these authors also state that lead has a "devastating effect on reproduction and pregnancy since it most commonly causes sterility or early spontaneous abortion. It has been clearly shown that lead crosses the human placenta and may cause untoward effects in the fetus (Karlog and Moller [2]). Around the beginning of this century it was recognized that women employed in the lead trades often produced live-born infants who were small, weak, and neurologically damaged (Cantarow and Trumper [3]; Angle and McIntire [4])."

The detailed exposure pathways contributing to lead burdens in a receptor are shown in Figure 2. It was the objective of this study to quantitate these pathways and, thus, to determine total exposure and its variability among individuals and populations. Additionally, the relations between exposure, dose, uptake, and effects were assessed. The diagram in Figure 3 illustrates the pathways of lead within a critical receptor. These pathways were assessed to determine the best indices of body lead burdens.

A hypothetical example of comparative lead body burdens based on calculated absorption is shown in Figure 4. It should be noted that this comparison cannot be correlated with blood-lead levels, and only represents an unknown total body distribution after absorption, but prior to any excretion. From this illustration, however, it is clear that young children must be given top priority in designing a viable monitoring system for lead.

In spite of the availability of an impressive information base, the pathways leading to and within the critical receptor (Figures 2 and 3) cannot be quantitated without additional substantial investments in research and monitoring. One result of this lack of quantification is that current review documents tend to overestimate the contributions of leaded paint chips and to underestimate the importance of airborne lead which continually settles out on all surfaces and is available for resuspension and subsequent inhalation and ingestion.

Once sound integrated research monitoring system concepts are developed and applied to environmental lead surveillance, as well as for other pollutants, it will be possible to further delineate areas of concern, to provide reliable trend and research data, and to establish efficacious and economical control measures.

LEAD EXPOSURE PATHWAYS TO CRITICAL RECEPTOR

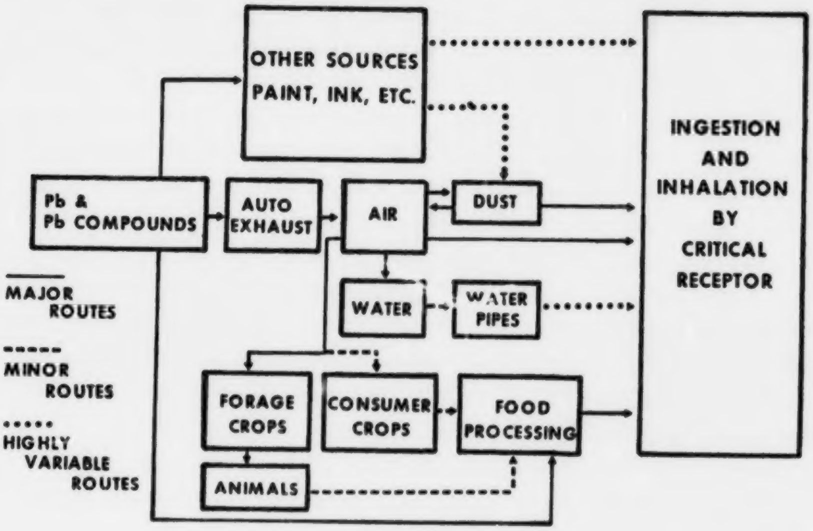

OTHER SOURCES
PAINT, INK, ETC.
Pb &
Pb COMPOUNDS
AUTO
EXHAUST
AIR
DUST
WATER
WATER
PIPES
FORAGE
CROPS
CONSUMER
CROPS
FOOD
PROCESSING
ANIMALS
INGESTION
AND
INHALATION
BY
CRITICAL
RECEPTOR
MAJOR
ROUTES
MINOR
ROUTES
HIGHLY
VARIABLE
ROUTES

FIGURE 2.

PATHWAYS OF LEAD IN CRITICAL RECEPTOR

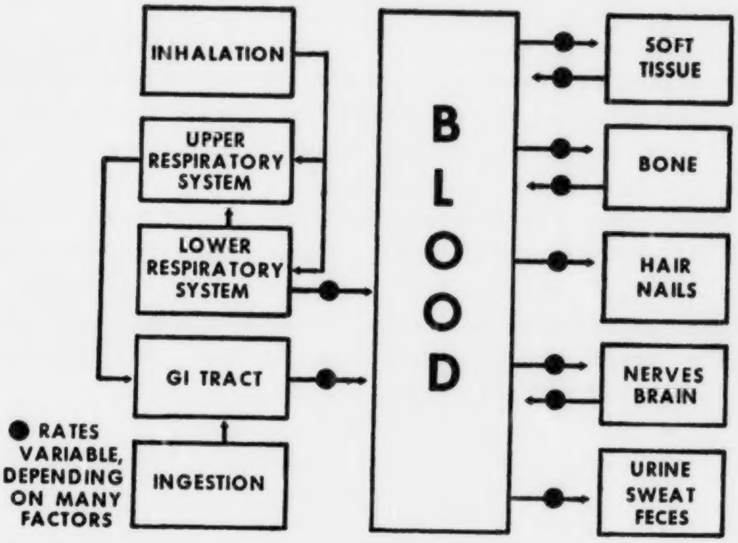
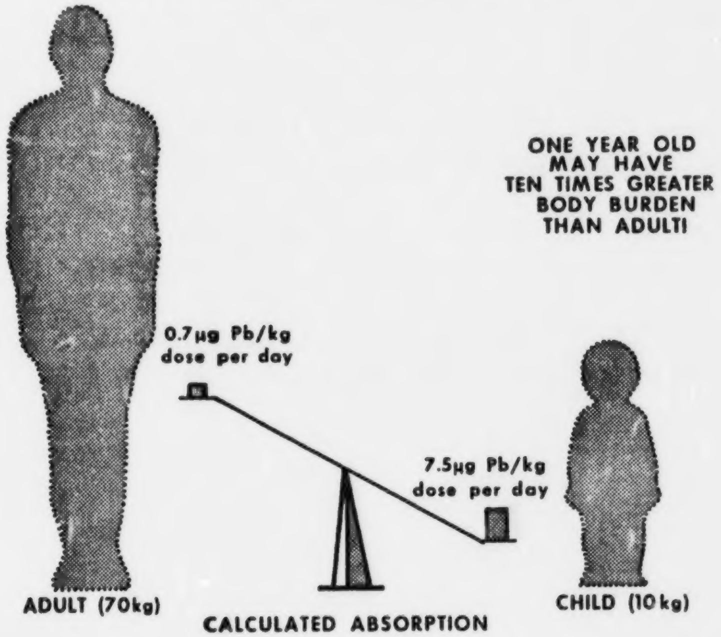

INHALATION
UPPER
RESPIRATORY
SYSTEM
LOWER
RESPIRATORY
SYSTEM
GI TRACT
INGESTION
B
L
O
O
D
SOFT
TISSUE
BONE
HAIR
NAILS
NERVES
BRAIN
URINE
SWEAT
FECES
● RATES
VARIABLE,
DEPENDING
ON MANY
FACTORS

FIGURE 3.

HYPOTHETICAL LEAD BODY BURDEN COMPARISON BETWEEN ADULT AND CHILD



ONE YEAR OLD
MAY HAVE
TEN TIMES GREATER
BODY BURDEN
THAN ADULT!

CALCULATED ABSORPTION

Daily Intake	Lead Absorbed	Daily Intake	Lead Absorbed
Food - 300 μg	30 μg (10%)	Food - 130 μg	65 μg (50%)(a)
Water - 20 μg	2 μg (10%)	Water - 10 μg	5 μg (50%)(a)
Air - 2.5 μg (23 m^3)	21 μg (37%)	Air - 2.5 μg (6 m^3)	5.5 μg (37%)
TOTAL	±53 μgPb	TOTAL	±75.5 μgPb

$\frac{53\ \mu\text{gPb}}{70\ \text{kg man}}$ = 0.7 μgPb/kg dose per day to man

$\frac{75\ \mu\text{gPb}}{10\ \text{kg child}}$ = 7.5 μgPb/kg dose per day to child

---

(a) Based on study entitled "The Uptake and Excretion by Children of Lead and Other Contaminants" by Alexander et al. (1973). Also refer to "Intestinal Lead Absorption" by Karhausen (1973) for further information.

Figure 4

REFERENCES

1 Palmisano, P. A., Sneed, R. C., Cassady, "Untaxed Whiskey and Fetal Lead Exposure," J. Pediatrics, Vol. 75 No. 5., 1969.

2 Karlog, D., Moller, K. O., "Three Cases of Acute Lead Poisoning," Acta Pharmacol., Vol. 15 No. 8., 1968.

3 Cantarow, A., Trumper, M., Lead Poisoning, Baltimore, The Williams and Wilkins Company, p. 143, 1944.

4 Angle, C. R., McIntire, M. S., "Lead Poisoning During Pregnancy," Am. J. Dis. Child, Vol. 108:436, 1964.

INTEGRATED ASSESSMENT OF HEALTH EFFECTS OF AIR POLLUTION

L. R. BABCOCK JR.[+], N. L. NAGDA[+] AND A. T. ROSSANO[++]

[+] University of Illinois, Chicago and Argonne National Laboratory, USA

[++] University of Washington, USA

ABSTRACT

This presentation is directed to individuals who seek a comprehensive methodology for assigning air quality management priorities. A comprehensive system of indices is being developed which relates population exposure and health-related damage back to individual emission sources. The system will be used to rank source severities and at the same time will enable improvement of the experimental design of health effect studies. This presentation addresses one aspect of our continuing research: a simulation names "popex" is described which integrates earlier air-quality-index concepts with population exposure considerations.

The prime purpose of most air quality management strategies is to reduce the health risk to exposed human populations. The situation is complex with many kinds of sources, pollutants, and human receptors, all ties together by uncertain source-receptor pathways (1). Much needed is a quantitative framework which considers both costs of improving air quality as well as health and other damages associated with exposure of people to various air pollutants.

A limited number of studies analyzing direct and indirect control costs are available, but much less is known about damages caused by air pollution exposure. Many more health-effect studies *are needed before all facets of health damages due to air pollution can be defined. Generally, the individual studies that are presently available are restricted to single pollutants and are quite limited in terms of time-concentration variables. Needs are well recognized, and health effects studies are increasing, both in number and in level of sophistication.*

However, health effect data are not in themselves sufficient for relating emissions to health damages. One of several missing links is knowledge of exact pollutant concentrations received by human receptors as a function of time.

1. Introduction

Despite complexities and uncertainties, the need for an overall framework for assessment of integrated air pollution health effects is quite evident. Such a framework should be able to relate air pollution damages back to sources and should enable the ranking of source severity. The system would be expected to have some gaps wherein the relationships between some parameters are not known rigorously. In such instances, our strategy would be to use the available not-so-rigorous relationships until better information is available.

It may seem unusual to describe uncertainty so early and prominently in our paper, but it seems appropriate that the complexities of the undertaking be defined before presenting our model:

Pollutant transport mechanisms. Dispersion models with various levels of sophistication can be employed for the estimation of pollutant concentrations at receptor sites. Such models all require some form of calibration and have never been verified for complex urban situations. Compounding the difficulty, the large amounts of prerequisite meaningful meteorological data are virtually non-existent.

Interaction of pollutants. Pollutants react with other pollutants as well as with other materials. These reactions could produce more- or less-potent intermediates, leading to particulate matter which is eventually removed from the atmosphere, or to innocuous decay end products, such as carbon dioxide and water. Some systems are understood better than others. Oxidant formation has been subjected to intensive study, but similar work is just beginning to shed light on the mechanisms involved in the atmospheric conversion of sulfur dioxide and nitrogen oxides into possibly-more-toxic particulate sulfates and nitrates. None of the systems are understood sufficiently to permit the reliable prediction of actual atmospheric reaction rates. Recent research has tended to identify increasing complexity rather than develop useful models with general applicability.

Source-receptor geometry. In order to arrive at an estimate of pollutant dosage, source-receptor geometry must be considered. Residences are not distributed evenly throughout a region, and inhabitants do not spend all their time near home. Indoor-outdoor pollution differentials add further complexity.

Health effects. There are numerous health-related uncertainties.

Questions remain for even the more-direct adverse health effects such as emphysema and bronchitis, and thus, with the present state of our knowledge, quantification of probable indirect psychological or genetic effects seems almost impossible.

2. Rationale and Approach

Our approach is stepwise, starting with simplistic relationships, adding complexity as it seems justified.

An emission inventory serves as the starting point for ranking sources of air pollution; early evaluations indicated that the automobile was responsible for over 50 percent of the gross mass of emissions within many urban regions. Based upon this evidence, control programs were initiated within the USA and elsewhere. However, an emission inventory ignores both the relative toxicity of the pollutants as well as the source-receptor geometry,

Our next step was to develop an air quality index which considered sulfur dioxide, nitrogen oxides, carbon monoxide, particulate matter, hydrocarbons, and oxidant. The index, called pindex, enabled the direct comparison of multi-pollutant emissions. When toxicities are considered, automotive pollution is reduced significantly in relative importance. Details as to the development and application of pindex are described elsewhere (2). Pindex concepts have been employed in a 20-category cost-benefit analysis (3) and have also been extended to address ambient air quality (4).

Pindex adjustment multiplies the meaningfulness of an emission inventory, but the emission-directed pindex ignors factors involving source-receptor relationships. General land-use-people-pollution relationships have been addressed elsewhere (5,6); our first generation attempt at specifically integrating population exposure with pindex is described below:

3. Population-Adjusted-Pollution Index: Popex

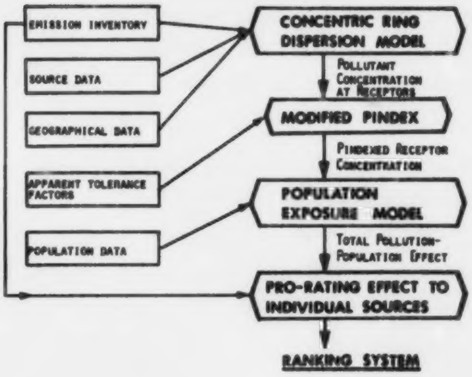
The pindex methodology is being expanded to incorporate important considerations such as meteorological dispersion modeling and variables related to the source-receptor distances and population distribution. We call this population-adjusted-pollution index, "popex", for short.

Utilization of a complex and time-consuming meteorological model in popex could have increased the sophistication of the methodology. But we have chosen to first construct and evaluate a simple "pseudo-meteorological" model. The concentric ring, gaussian plume model has a level of sophistication beyond that of a box model, and we feel it well balances with the present levels of complexity and accuracy of other aspects of the methodology.

The geographical area considered in popex is the Air Quality Control Region (AQCR), and in our present version, counties are the smallest areal elements considered. Our initial application will evaluate sources within the Chicago AQCR which consists of 8 million people distributed among eleven counties.

First calculated in popex are total dosages of the six pollutants reaching each of the counties from all the sources within the AQCR. Then the levels of each pollutant, including oxidant formed by simulated photochemical reactions, are combined into single effect numbers by pindex. Finally, the percent contributions of individual sources (to the total pollution-population exposure) are used to assign a priority-ranking to each source. The diagram summarizes the popex model (7).

POPEX FLOW DIAGRAM


EMISSION INVENTORY
SOURCE DATA
GEOGRAPHICAL DATA
APPARENT TOLERANCE FACTORS
POPULATION DATA
CONCENTRIC RING DISPERSION MODEL
POLLUTANT CONCENTRATION AT RECEPTORS
MODIFIED PINDEX
PINDEXED RECEPTOR CONCENTRATION
POPULATION EXPOSURE MODEL
TOTAL POLLUTION-POPULATION EFFECT
PRO-RATING EFFECT TO INDIVIDUAL SOURCES
RANKING SYSTEM

4. Discussion and Conclusions

The popex model yields the expected results when applied to contrived situations. However, it will be necessary to carefully evaluate the model with actual geographically-specific data; we look forward to presenting in the near future, our assessment of the 1600 sources within the Chicago AQCR.

Our preliminary results indicate that short-distance source-to-receptor exposures account for the dominant fraction of total air pollution damages. (The population affected may be low, but the exposure-per-person is very high.) Thus, small errors in this part of the simulation may yield large errors in the overall results. For example, our first-generation source-receptor configuration locates all the receptors in a county at a single distance or radius from the point sources, at a "ring of average exposure". The correct location of this ring is a complex function of stack height, population distribution, and meteorological variables. The assumptions made must receive careful appraisal.

With popex, we are attempting to integrate population exposure parameters and toxicity of pollutants to arrive at a system for hazard-based ranking of sources. Our present version must be considered a "first generation" model. Most of the complex variables mentioned in this paper have not yet been included in popex. Considerable revision, extension, and verification will be required before popex can become a meaningful policymaking tool. Toward this goal, we seek communication and interaction with others involved in similar endeavors (7).

5. Acknowledgements

Gratefully acknowledged are the computer services provided by the Computer Center at UI, Chicago Circle, and the continuing financial support provided by the U. S. Environmental Protection Agency (Grant R-802111) and by the National Science Foundation (RANN program AG-352 through Argonne National Laboratory and Grant GK-27772 through the University of Illinois).

References

1. A. T. Rossano, Jr., ed., Air Pollution Control: Guidebook for Management, E.R.A., Inc., Stamford, Connecticut, 1969.
2. L. R. Babcock and N. L. Nagda, "Indices of Air Quality," Indicators of Environmental Quality (W. A. Thomas, Ed.), Plenum Press, New York, 1972, pp. 183-197.
3. L. R. Babcock and N. L. Nagda, "Cost Effectiveness of Emission Control," Journal of the Air Pollution Control Association, 23, March 1973, pp. 173-179.
4. W. A. Thomas, L. R. Babcock and W. D. Shults, Oak Ridge Air Quality Index, (ORNL-NSF-EP-8), Oak Ridge National Laboratory, Tennessee, September 1971.
5. N. L. Nagda and L. R. Babcock, "Integration of Land Use Considerations into Air Quality Management Strategies," Papers and Proceedings Third Pacific Regional Science Conference, August 1973, Honolulu, Tokyo University Press (to be published, 1974).
6. D. V. Lamb, F. I. Badgley and A. T. Rossano, "A Review of Diffusional Modeling Techniques for Predicting Air Quality with Relation to Transportation," study prepared for Washington State Highway Commission (Contract 63-1062), Seattle, Washington, 1973.
7. Additional information may be obtained from the authors. Write Prof. L. R. Babcock, Jr., School of Public Health, University of Illinois, P. O. Box 6998, Chicago, Illinois 60680, USA.

MEXICO CITY'S PINDEX LEVEL

H. BRAVO A., M. E. ESPINOSA, A. C. LOWE AND S. SALAZAR

Instituto de Geofísica, Universidad Nacional Autónoma de México
Mexico, D.F.

ABSTRACT

Up to now, an attempt to evaluate Mexico City's air pollution as a total has not been made. A more comprehensive way of evaluation, where concentration as well as tolerance limits are interrelated is needed. Also, the effect of solar radiation has never been considered as a direct parameter in the dynamics of the air pollution problem.

Due to the special location of Mexico City, in an altitude of 2,268 m above sea level, and a latitude of 19°20' North, we strongly believe that solar radiation has to be considered if a good understanding of air pollution is desired.

The use of the Pindex approach will be useful in the study of the expected epidemiological and health effects as a result of air pollution and it will, as well, be a tool for the selection of control strategies.

Preceding page blank

In order to evaluate the existing air pollution monitoring data, the tendency in Mexico is by unit mass. It is well known that different air pollutants have different toxicity levels, based on mass-time relationships. Babcock[1,4] introduced these tolerance levels and other parameters to develop an index. If we follow this new approach, we will be able to calculate a similar pollution index, although not 100% correct for Mexico City and other Mexican cities, it would, at least, be the beginning to point out the need for a new way to evaluate the existing data and obtain more realistic regulations and control policies.

Mexico City is located in the southwestern corner of an elevated basin (2,268 m above sea level), at a latitude of 19°20' North, with a very high incidence of calms and vertical gradient inversions of temperature during the year[2]. The above parameters make of Mexico City a unique case of study regarding air pollution and its effects.

The City is part of the metropolitan area, with a population close to nine million inhabitants, about 700,000 vehicles, and containing about 20.5% of the total industrial activity of the country. As Mexican petroleum crudes are very high in sulphur, the oil fuel used contains between 3 to 4% in weight of sulphur.[3]

The reliable air quality data in Mexico City is, at this moment, quite limited, but most of the information used in this paper, although short in number, has a high degree of confidence. Some of the data used is the only existing one; its source is quoted in the paper.

The method used here is the one suggested by Babcock et al.[1,4] to estimate the total air pollution pindex, although we feel that for Mexico City a more complex index, with specific tolerance levels and the introduction of several new parameters is needed.

Table No. I shows the air quality data used for the development of Mexico City's Pindex and their corresponding pindex levels.

Table No. II shows the method carried out, in order to obtain the individual pindex levels and the total index from the given information.

Mexico City's data was reduced when it was necessary, using Larsen approximation.[7]

The tolerance factor used for particulate matter was derived from the primary 24 hour standard[7].

For SO_2, the tolerance factor was derived from the secondary 3 hour standard[7].

The NO_2 factor was the one used by Babcock, but extrapolated to 1 hour.[4]

Carbon monoxide's factor was derived from the 1 hour standard.[7]

The hydrocarbon's factor used was the one employed by Babcock[1,4].

The oxidant's factor was derived from the standard used by Larsen[7].

Table III lists the pindex obtained for Mexico City and some U.S.A. cities. The pindex for the U.S.A. cities was recalculated using the concentrations reported by L.R. Babcock[1], and the same tolerance factors used for Mexico City's Pindex.

It is clear from Table III that Mexico City ranks first, with a typical photochemical problem in addition to a high concentration of particulate matter.

Once more, this index for Mexico City is just a preliminary approach, which shows the need to obtain specific tolerance factors for pollutants at Mexico City's conditions.

Besides, regulations and control strategies have to be reviewed and designed based on a specific index for Mexico City.

TABLE NO. I
Mexico City's Air Pollutants

Concentrations and Corresponding Pindex levels

	P.M.* ($\mu g/m^3$)	SO_2 (ppm)	NO_x (ppm)	CO (ppm)	HC (ppm)	Oxidant (ppm)
Concentrations	227	0.021	0.113	13.4	10.52	0.048
Pindex levels	1.060	0.030	0.049	0.290	0.27	0.750

*P.M. = particulate matter

TABLE NO. II
Pindex Calculations

Available information for Pindex Calculation

Particulate matter[5]	(PM)	= 277 $\mu g/m^3$
Sulfur Dioxide*	(SO_2)	= 42.26
Nitrogen oxides*	(NO_x)	= 132.5
Carbon monoxide[5]	(CO)	= 11.655
Hydrocarbons[6]	(HC)	=5231
Oxidant*	(O_3)	= 71.1
Solar radiation**	(SR)	= 591 $cal/cm^2 day$

Convert reactants to $\mu mol/m^3$
NO_x = 132.5/46 = 2.88 $\mu mol/m^3$
HC = 5231/16 = 326.9
O_3 = 71.1/48 = 1.48

Determine limiting reactant for oxidant synthesis (NO_x or HC): NO_x is limiting

Create oxidant:
O_3 = 0.0006 x SR x (limiting reactant)
O_3 = 0.0006 x 591 x 2.88 = 1.02 $\mu mol/m^3$

Determine total oxidant and excess HC and NO_x
O_3 = 1.48 + 1.02 = 2.50 $\mu mol/m^3$
HC = 326.9 - 1.02 = 325.88
NO_x = 2.88 - 1.02 = 1.86

Convert reactants back to weight basis
O_3 = 2.50 x 48 = 120.00 $\mu g/m^3$
HC = 325.9 x 16 = 5214.00
NO_x = 1.86 x 46 = 85.56

Apply tolerance factors
PM = 277/260 = 1.060
SO_2 = 42.26/1330 = 0.030
NO_x = 85.56/1720 = 0.049
CO = 11655/40000= 0.290
HC = 5214/19300 = 0.027
O_3 = 120/160 = 0.750

Determine Synergism term (SYN)
SYN = SO_2 or PM (whichever is smaller)
SYN = SO_2 = 0.03

Sum terms to determine pindex
Pindex = PM + SO_2 + NO_x + CO + HC + O_3 + SYN
Pindex = 2.48

---

* Departamento de Contaminación Ambiental. Instituto de Geofísica, U.N.A.M., México

** Departamento de Radiación Solar, Instituto de Geofísica, U.N.A.M., México.

TABLE NO. III

Mexico City* and U.S.A. cities**
Pindex levels

	P.M.	SO_x	NO_x	CO	HC	Oxidant	Total***
Mexico City	1.060	0.030	0.050	0.290	0.270	0.750	2.48
Chicago	0.477	0.307	0.115	0.345	0.101	0.531	2.18
Los Angeles	0.450	0.044	0.144	0.316	0.134	0.987	2.12
Philadelphia	0.590	0.170	0.066	0.190	0.067	0.350	2.04
Denver	0.480	0.020	0.057	0.227	0.080	0.570	1.45
San Francisco	0.260	0.020	0.110	0.090	0.100	0.650	1.25
San Diego	0.260	0.020	0.040	0.080	0.200	0.510	1.13

* Calculated from existing data. Annual average.
** Annual average
*** This term includes the synergistic effect.

REFERENCES

1 Lyndon R. Babcock, Jr., "A combined pollution index for measurement of total air pollution", J. Air Poll. Control Assoc., 20 (10):653 (October 1970).

2 H. Bravo, A. et al., "Contribution of stationary combustion sources to the horizontal sulphur. Dioxide concentration in the Mexican Valley. Paper No. 68-35. Presented at the 68th Annual Meeting APCA, Saint Paul Minnesota, June 1968.

3 Serie Estudios/1. Medio Ambiente Humano Problemas Ecológicos Nacionales. Secretaría de la Presidencia. Cuadernos de Documentación. Serie Estudios/Núm.1. Segunda Edición Ampliada. Pág. 42, 1972.

4 Babcock, L.R. and Nagda, N.L., Letter to the Editor, "Rating of Pollutants by Effect", J. Air Poll. Control Assoc. (22) 9:727, (September 1972).

5 Bravo, H., Corona, L., "La Contaminación atmosférica y su relación con el flujo de vehículos en la Ciudad de México". Inst. de Ingeniería, 227. Mayo 1969. México.

6 Panivino, N.,"Determinación de Hidrocarburos Totales en el aire por el Método de Ionización de Flama", Tesis, Facultad de Ciencias Químicas, U.N.A.M., (desarrollada en el Instituto Mexicano del Petróleo), México, D. F., 1973.

7 Larsen, R.I., "A mathematical model for relating air quality Measurements to Air Quality Standard, U.S. Environmental Protection Agency. Research Triangle Park, North Carolina, November 1971.

A METHOD FOR SIMULATING THE TRUE HUMAN EXPOSURE OF CRITICAL POPULATION GROUPS TO AIR POLLUTANTS

WAYNE R. OTT[+] AND DAVID T. MAGE[++]

+ Environmental Protection Agency, Washington D.C., USA

++ San Jose State University, California, USA

ABSTRACT

There are serious problems in obtaining an accurate assessment of the true population exposure to air pollutants. In the United States, the primary means for monitoring air quality is by measurements at fixed locations in urban areas, or air monitoring stations. It is becoming increasingly apparent that data from such stations provide a relatively poor measure of the true exposure of members of the general public to air pollutants, because these stations are not necessarily located where the public is exposed to the highest concentrations.

To demonstrate a method to obtain a more representative measure of the human exposure of a critical population group - pedestrians and shoppers - a technique was developed for simulating the true exposure of pedestrians to carbon monoxide (CO) by collecting integrated CO samples over the routes that they walk. A total of 425 of these simulated exposure samples (SES) were collected on congested downtown streets in a major urban area. The results were compared statistically with conventional measurements from a nearby fixed monitoring station. Significant differences were observed between these two sampling methodologies - fixed and SES - and the significance of these findings for setting air quality standards is discussed.

1. Introduction

Serious problems arise in accurately assessing the true human exposure to air pollutants. In the United States, the usual practice for monitoring air quality is to measure selected air pollutants (carbon monoxide, hydrocarbons, sulfur dioxide, particulates, etc.) at fixed locations in each urban area. Unfortunately, concentrations at these air monitoring stations are not necessarily representative of concentrations to which a significant proportion of the population actually may be exposed.[1,2,3] This occurs because the stations are not always located where concentrations are highest and where large numbers of people also congregate. The most serious problems arise when monitoring stations are located high--for example, on the 5th or 7th floor of a downtown building--or at the outskirts of a city's central business district. Such monitoring locations are common in the United States.

2. U.S. Air Quality Standards

In any environmental monitoring effort, the first step is to decide whose exposure the data are intended to measure. In the United States, national ambient air quality standards have been adopted for the major air pollutants. The standards for carbon monoxide (CO), for example, specify the following concentrations and averaging times:*

35 ppm CO for 1 hour
9 ppm CO for 8 hours

The U.S. standards "are not to be exceeded more than once a year" in the "ambient air," which is defined as "that portion of the atmosphere, external to buildings, to which the general public has access."

The current U.S. definition excludes special occupational groups (traffic policemen, taxi drivers, etc.), but it apparently includes shoppers, housewives, businessmen, school children, or any others who are outdoors and are, thereby, exposed to ambient air pollutants.

---

*One ppm (part per million by volume) is equal to 1.14 mg/m^3 at 24°C and 1 atmosphere pressure.)

3. Methodology of Study

In our study, we define a "critical population" to be any subset of the general population who share common characteristics and, as a result, are exposed to similar atmospheric concentrations. To demonstrate how the exposure of one particular critical population may be more adequately monitored, we focused on one critical population--downtown pedestrians.

To determine their true exposure, we developed a Simulated Exposure Sampling (SES) technique. In this approach, the investigator walks along the sidewalk while collecting an ambient air sample in a specially prepared, plastic bag. The intake tube is held at "breathing height," and the bag is filled by a small, portable electric pump.* The result is a "linear average" of CO concentration over several city blocks or more. Enough samples are collected to provide a statistically valid measure of the human exposure along a given route and over a designated averaging time.

We collected 425 SES bags on 21 days in midwinter in the downtown area (South First Street) of San Jose, California. Each bag was filled continuously during walks over each of four different routes. Generally, each sample required about 5 minutes. While walking, the investigator generally maintained the same pattern of movement as pedestrians--for example, halting for traffic signals.

4. Results of Study

The SES values were significantly higher than values simultaneously recorded at an official air monitoring station approximately 2.6 kilometers from the downtown area (Table 1). The 425 SES values averaged 9 ppm--1.6 times the average value of 5.5 ppm recorded at the air monitoring station. Individual SES values ranged as high as 10 times the monitoring station

---

*Breathing height was defined as 5 ft. ±1/2 ft. above the ground. Bags were constructed of Mylar and required about 5 minutes to fill. All bags were analyzed in a central laboratory by nondispersive infrared absorption. The pump was powered by nickel-cadmium batteries and was constructed with inert Teflon parts.

TABLE 1

RESULTS OF SIMULATED EXPOSURE SAMPLING (SES) IN DOWNTOWN SAN JOSE, GROUPED BY DATE

Date	No. of Samples	Sampling Period, hrs.	CO Concentration, ppm*				Ratio (SES/Mon.)
			Simulated Exposure Samples		Monitored Values		
			Mean	Std. Dev..	Mean	Std. Dev.	
11/10/70	27	9.0	7.4	2.2	5.4	1.0	1.4
11/11/70	10	3.5	4.5	3.8	2.1	0.1	2.1
11/17/70	18	5.5	10.0	3.3	7.9	2.4	1.3
12/11/70	36	9.0	8.6	3.1	5.5	1.3	1.6
12/22/70	40	9.0	13.0	5.9	4.4	2.2	3.0
12/24/70	40	8.5	14.2	5.9	6.2	1.9	2.3
12/30/70	41	8.0	9.1	2.7	5.6	1.5	1.6
1/05/71	8	2.0	6.4	1.6	5.8	3.5	1.1
1/06/71	4	0.5	5.2	1.3	5.2	0.6	1.0
1/07/71	11	2.5	8.8	3.2	4.3	0.5	2.1
1/18/71	12	3.5	10.3	3.5	7.3	2.1	1.4
1/19/71	8	1.5	7.5	2.5	7.0	0.6	1.1
1/21/71	10	1.5	5.3	1.6	5.2	0.5	1.0
1/26/71	18	4.0	9.9	3.0	7.6	1.8	1.3
1/27/71	6	1.0	11.4	2.8	8.5	2.3	1.3
1/28/71	30	6.5	8.8	2.9	6.8	1.7	1.3
1/29/71	9	1.5	8.3	2.3	5.9	2.0	1.4
2/03/71	10	2.0	5.3	1.8	6.2	1.5	0.8
2/04/71	12	2.0	7.0	4.0	5.8	1.3	1.2
2/24/71	34	7.5	5.2	2.1	2.4	0.6	2.1
3/19/71	41	8.5	7.6	3.1	5.0	1.1	1.5
Overall Results:	425	97.0	9.0	4.4	5.5	2.1	1.6

*ppm = parts per million by volume.

values. The correlation coefficient between SES values and official monitoring station values was positive, but low ($r = +0.20$).

The seven dates on which SES values were collected over at least 8 full hours are of particular interest because the U.S. ambient air quality standard specifies an 8-hour period.* On these dates, the 8-hour average of SES values ranged between 1.4 and 3 times the values observed at the air monitoring station (Table 2). Application of the sign test found the difference in means to be statistically significant in all seven cases ($p < 0.01$).

On three of these dates, downtown pedestrians or shoppers spending 8 hours in the area were exposed to CO concentrations above the U.S. standard of 9 ppm, while the monitoring station reported values below the standard. On the two dates with highest concentrations, there was considerable variance in the SES values (Figures 1 and 2). These were dates of heavy downtown traffic, and the SES values, which are indicative of concentrations to which downtown pedestrians are actually exposed, were strikingly greater than values reported at the same time at the official air monitoring station.

SES data also illustrate the feasibility of obtaining true measures of the exposure of critical population groups with relative ease and economy by the SES approach.

5. Implications for Setting Air Quality Standards

In any given city, at any instant of time, actual pollutant exposures occur both above and below the values observed at a fixed monitoring station. Figure 3 shows a hypothetical distribution of 8-hour CO exposures for the population of a particular city during any given 8-hour period. The shaded area under the curve to the right of x^* is the probability that a given individual will be exposed to an 8-hour CO concentration greater than x^*.

---

*The average value of 30 or 40 discrete, 5-minute bag samples collected over an 8-hour period can be used as a valid estimate of the overall average during the period.

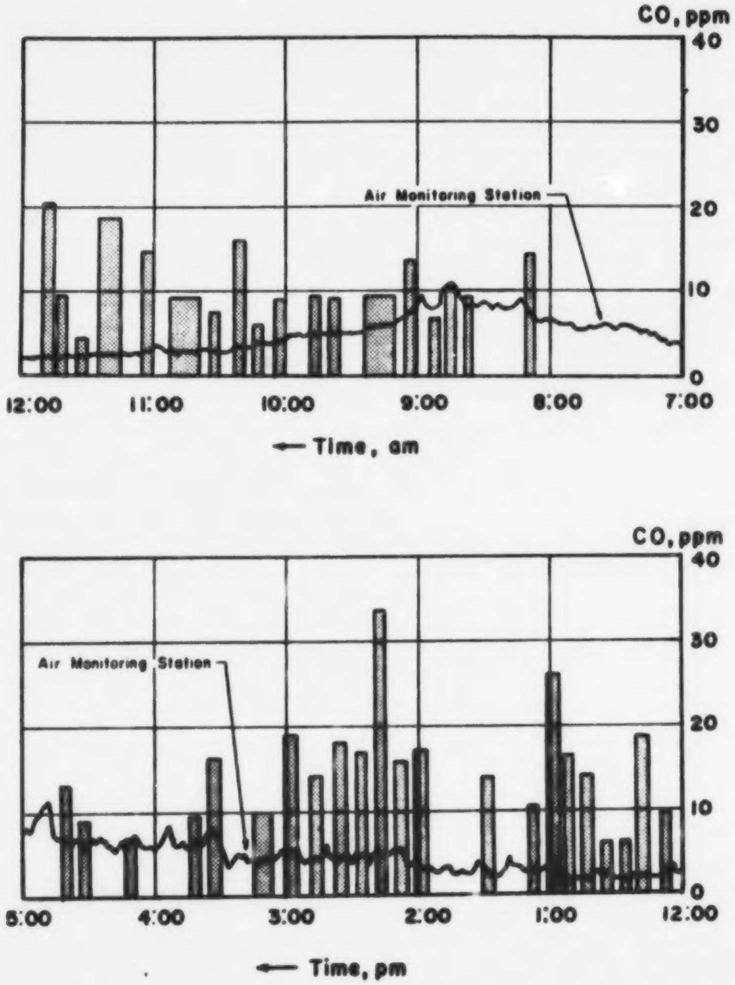
TABLE 2

RESULTS OF SIMULATED EXPOSURE SAMPLING (SES) OVER EIGHT-HOUR PERIODS IN DOWNTOWN SAN JOSE*

DATE	NO. OF SAMPLES	SIMULATED EXPOSURE SAMPLE (MEAN CO, ppm)	MONITORED VALUE (MEAN CO, ppm)	RATIO (SES/Mon.)
11/10/70	27	7.4 (± 0.9)	5.4 (± 0.4)	1.4
12/11/70	36	8.6 (± 1.1)	5.5 (± 0.4)	1.6
12/22/70	40	13.0 (± 1.9)	4.4 (± 0.7)	3.0
12/24/70	40	14.2 (± 1.9)	6.2 (± 0.6)	2.3
12/30/70	41	9.1 (± 0.9)	5.6 (± 0.5)	1.6
2/24/71	34	5.2 (± 0.7)	2.4 (± 0.2)	2.1
3/19/71	41	7.6 (± 1.0)	5.0 (± 0.3)	1.5

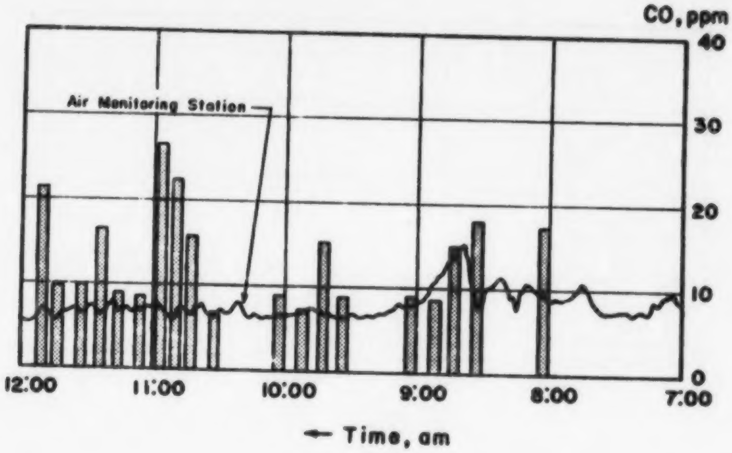
---

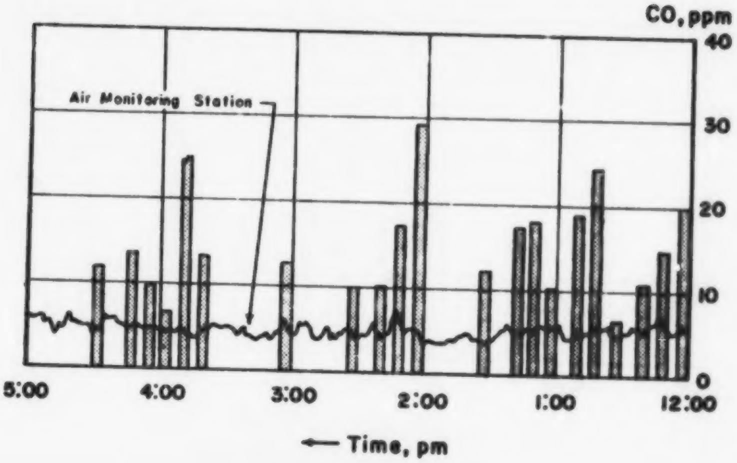
*VALUES IN PARENTHESES ARE 95% CONFIDENCE INTERVALS.



DECEMBER 22, 1970

FIGURE 1. CONCENTRATION MEASURED BY SIMULATED EXPOSURE SAMPLING ON DOWNTOWN FIRST STREET IN SAN JOSE, CALIF., ALONG WITH CONCENTRATION MEASURED AT THE AIR MONITORING STATION. (NOTE: TIME IS PLOTTED FROM RIGHT TO LEFT.)





DECEMBER 24, 1970

FIGURE 2. CONCENTRATION MEASURED BY SIMULATED EXPOSURE SAMPLING ON DOWNTOWN FIRST STREET IN SAN JOSE, CALIF., ALONG WITH CONCENTRATION MEASURED AT THE AIR MONITORING STATION. (NOTE: TIME IS PLOTTED FROM RIGHT TO LEFT.)

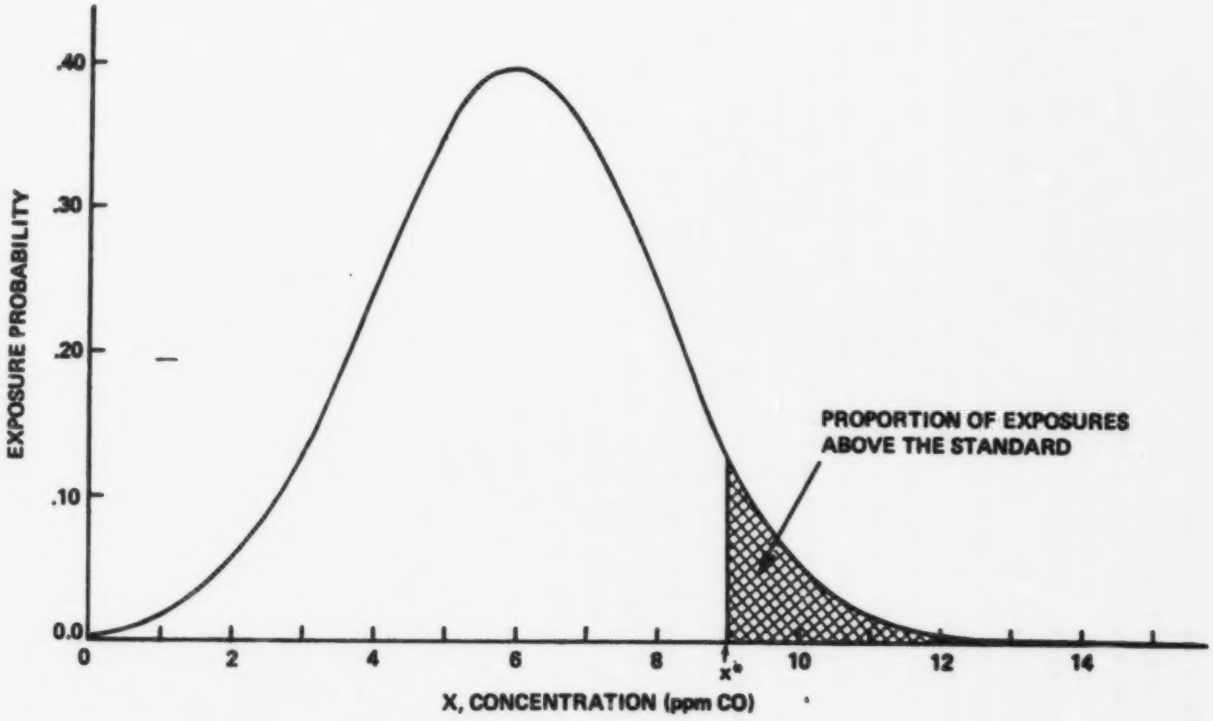


FIGURE 3. HYPOTHETICAL DISTRIBUTION OF CO 8-HOUR EXPOSURES IN A GIVEN CITY.

The area also may be interpreted as the proportion of the general population exposed to pollutant concentrations above x* during a particular 8-hour period. If, for example, x* is the U.S. CO standard of 9 ppm, the goal of air pollution control efforts would be to shift the curve as much as possible to the left, minimizing the area under the curve to the right of x*. With such a model, of course, some proportion of the population, however small, will always be exposed to concentrations greater than x*. This is why air quality standards should state more precisely the proportion of the population to which they are intended to apply. An ideal CO standard, for example, might state, "the value applies to the highest 5 percent of 8-hour exposures of the general population, which consists of ..." Or the standard might apply to the highest 20 percent of the exposures of a given critical population group, such as downtown pedestrians.

In our view, a more precise, probabilistic definition would permit designing monitoring networks that more faithfully reflect true human exposures.

REFERENCES

1. OTT, WAYNE R., "An Urban Survey Technique for Measuring the Spatial Variation of Carbon Monoxide Concentrations in Cities," Ph.D. Thesis, Department of Civil Engineering, Stanford University, Stanford, California, October 1971.

2. OTT, WAYNE R. and ELIASSEN, ROLF, "A Survey Technique for Determining the Representativeness of Urban Air Monitoring Stations with Respect to Carbon Monoxide," Journal of the Air Pollution Control Association, Vol. 23, No. 8, August 1973, pp. 685-690.

3. OTT, WAYNE R. and MAGE, DAVID, "The Representativeness of Urban Air Monitoring Stations with Respect to Carbon Monoxide," Proceedings of the Second Annual Environmental Engineering and Science Conference, Speed Scientific School of the University of Louisville, Louisville, Kentucky, April 20-21, 1972, pp. 379-394.

4. "National Primary and Secondary Ambient Air Quality Standards," Federal Register, Vol. 36, No. 84, April 30, 1971, Washington, D.C., pp. 8186-7.

PERSONAL AND INDOOR EXPOSURE METERS

A. P. ALTSHULLER AND ANDREW E. O'KEEFFE

Chemistry and Physics Laboratory, National Environmental Research Center, Environmental Protection Agency, Research Triangle Park, N.C., USA

ABSTRACT

Current community health studies generally have to utilize results of pollutant monitors in fixed or mobile sites to determine pollutant exposures of individual subjects. Pollutant exposures over 24-hour periods involve exposure not only to community pollutant concentrations, but also to commuter and indoor pollutant concentration levels. The exposures of a discrete and mobile group of subjects to community pollutant concentration levels are not readily derived from monitoring results at a limited number of fixed sites.

The limitations in the present situation can be resolved by the development of small portable "exposure meters" for measuring an individual's exposure to air pollutants. The individual in the study could carry the instrument and operate it at home, in a vehicle, office, laboratory, etc. Projects are being developed by the Chemistry and Physics Laboratory, National Environmental Research Center, RTP, for exposure meters and as an alternative simple portable samplers. Emphasis will be on measuring nitrogen oxides, sulfur oxides and oxidant. Because of the available capability to do carbon monoxide in blood samples, there is no current need for a carbon monoxide device. Particulate species such as sulfate and nitrate probably could be collected on appropriately designed mini-samplers.

Preceding page blank

A state of the art survey will be conducted, especially concerned with fine particulate species, noise and other environmental pollutants. This document will be used to develop the long-range program on exposure meters in the U.S. Environmental Protection Agency. The status of available personal monitors for physiological parameters will be evaluated by the Human Studies Laboratory, National Environmental Research Center, Research Triangle Park, N.C.

1. Introduction

Our present knowledge of the effects of pollutants on the human population is very largely based on estimates of the dosage received. These estimates are derived from measurements of pollutant concentrations at fixed sites, about and among which sites the individuals making up the population continually swirl in patterns so complex as to defy analysis. The Environmental Protection Agency is conducting a program to develop a capability for recording the exposure of individuals to selected pollutants, without placing constraints upon the subjects' normal activities. This paper will examine the several strategies available for approaching that ideal, and will consider the compromises demanded by each in the interest of practicality.

2. Physical Methods

2.1 Principle: A physical property of a gas is measured and related to concentration.

2.2 Scope: Spectral absorbance is the only physical property which current technology can measure with sufficient accuracy for the present application. The requirement of a very long optical path to attain parts-per-billion sensitivity appears to be incompatible with size constraints inherent in the term "personal exposure meter" and (because of the extremely precise collimation needed) with the inevitable exposure of such an instrument to inertial disturbances when carried on the person. In light of these limitations, absorbance methods have been given low priority in the present program.

3. Energy-Transfer Methods

3.1 Principle: Reaction of the pollutant of interest (usually with a second reactant) results in a transfer of energy quantitatively related to concentration.

3.2 Scope: Three major forms of such devices are presently known to exist:

3.21 Chemiluminescence: Gas molecules interact with production of a new molecule in an excited state. Excited molecule relaxes to ground-state with release of light energy:

$$A + B \longrightarrow C^*$$

$$C^* \longrightarrow C + h\nu$$

3.22 **Fluorescence**: Gas molecule absorbs light energy of a specific wavelength and is raised to an excited state. This relaxes to ground-state with release of light energy of (ordinarily) greater wavelength:

$$A + h\nu_{\gamma} \longrightarrow A^{*}$$

$$A^{*} \longrightarrow h\nu_{\gamma'}$$

3.23 **Electrochemical**: Gas molecule is oxidized (or reduced) at an electrode of a galvanic cell, transferring electrical energy to (or from) the opposing electrode:

$$A^{o} \dashrightarrow A^{+} + e$$

4. Sorption Methods

4.1 **Principle**: A sorbent collects the gas of interest at a rate dependent upon concentration. Subsequent desorption and measurement of the gas (or of a stoichiometrically related product) is usually performed in an off-site laboratory.

4.2 **Scope**: The great majority of pollutant gas measurement methods in use a few years ago were of this type. Classic examples would be the lead candle method for SO_2 and iodometric methods for ozone.

5. Research Strategy

5.1 **General Considerations**: Ideally, the device that is sought will be the size of a pocket radio receiver, and will store within itself a continuous record of the instantaneous concentrations of a given pollutant experienced over an extended sampling period - say 24 hours. It should have sufficient sensitivity to detect the pollutant at or near background levels, and should be free from interference from other substances likely to be encountered in an urban atmosphere. Unit cost must be kept at a level compatible with eventual use on a scale sufficient to support meaningful health-effect studies.

It is apparent that the above ideal will not be reached in a single step. Thus, we must choose those parameters that can best be compromised with reasonable assurance that either (a) later developments will eliminate the compromise, or (b) health-effect studies will not be rendered impractical. On such considerations, the ideal requirements pertaining to size and to time-resolution of educed data have been considerably liberalized so that a start can be made on assembling and evaluating prototype devices representative of the several types of methods previously discussed.

Initial prototypes are expected to be no larger than a briefcase in size, and to be capable of measuring the integrated average concentration of a pollutant for a period of time in the range 0.01-1.0 day.

5.2 Specific Plans for Initial Phase

5.21 Ozone: The potential of continuous instrumentation will be evaluated through the medium of a miniaturized ethylene-ozone chemiluminescence device. It is expected that this will include substitution of a less volatile substance for the ethylene, thus obviating the need for a pressurized cylinder. A parallel effort will examine the feasibility of reacting ozone with a solid organic substrate to form a metastable adduct that subsequently undergoes chemiluminescent decay upon heating.

5.22 Sulfur Dioxide: A commercially available electrochemical cell designed for measurement of ambient SO_2 will be miniaturized and provided with integrating electronics, as a candidate method. Also, an efficient sorbent will be identified, whose SO_2 adduct can later be thermally decomposed, the product being measured with a flame photometric sulfur detector.

5.23 Nitrogen Dioxide: Miniaturization of chemiluminescence instrumentation for NO_x is possible, but has the drawback that power is required to convert NO_2 to NO. Hence, the choice will probably go to an electrochemical device. The alternate method will involve sorption, subsequent thermal desorption, and eventual measurement through chemiluminescence.

6. General

Wherever possible, especially in the sorption methods outlined above, the need for accurately metering the air sample will be eliminated by interposing between sample and sensor a membrane permeable by the gas to be measured. This renders the sensor responsive to partial pressure of the analyte rather than to the absolute quantity contained in a sample of known volume. Relief from the requirement of a precision metering pump will greatly simplify the construction of a miniature instrument. We are also assessing, by means of aerodynamic modelling calculations, the magnitude of the error that will be introduced by eliminating the sample pump altogether and depending entirely on convection-diffusion for sample acquisition. Should the error prove to be acceptably small, this offers still another major simplification.

Development of personal monitors for particulate pollutants is a more difficult task. It is obvious that power must be supplied to move, separate and collect such materials; this fact alone poses major problems. Active work on this segment of the program will not start for another year or so.

7. Summary

EPA has an active program under way to provide personal monitoring devices for important pollutants. The instrument development program is being thoroughly coordinated with the efforts of the Human Studies Laboratory in order to assure optimum response to their needs. Our target is the narrow zone that lies between the inadequate and the over-sophisticated.

DIE AUTOMATISCHE UEBERWACHUNG DER KRAFTFAHRZEUGABGAS-IMMISSION IM ARBEITS- UND WOHNBEREICH

D. JOST, W. RUDOLF

Bundesstelle für Umweltangelegenheiten, Pilotstation Frankfurt/M
BRD

KURZFASSUNG

Ein vollautomatisches Messnetz zur Ueberwachung der Luftverunreinigung im Arbeits- und Wohnbereich der Stadt Frankfurt wird, ausgehend von den Erfahrungen bei der Schwefeldioxidüberwachung, zur Ueberwachung der kraftfahrzeugbedingten Abgase erweitert. Aufbauend auf langjährigen Messreihen verschiedener meteorologischer Grössen und von Luftverunreinigungen werden mit Hilfe von Abschätzungen atmosphärischer Ausbreitungsvorgänge die Luftverunreinigungsmessdaten bzw. Daten der luftverunreinigungsdosis für die Bewohner des betrachteten Raumes ermittelt.

Folgende Komponenten werden dabei erfasst: SO_2, CO, NO_x, *Oxidantien, Gesamtstaub, Blei und weitere Metalle im Staub.*

Mit Hilfe der Untersuchung der Korrelation verschiedener Luftverunreinigungen ist es möglich, die Zahl der Messstellen und die Zahl der zu untersuchenden Komponenten zu optimieren, wobei die Anforderungen folgender Untersuchungsziele zu berücksichtigen sind:
Flächen- und zeitbezogene Belastung mit Luftverunreinigungen, Trend verschiedener luftverunreinigender Komponenten, Smog-Warnung Optimierung von Messnetzen, Daten für epidemiologische Untersuchungen.

Aus diesen Aufgabenbereichen werden Untersuchungsergebnisse mitgeteilt, die auch eine Bilanzierung von Belastung durch Luftverunreinigungen und Erholung in Ballungsgebieten gestatten.

ABSTRACT

A fully automatic network for monitoring atmospheric pollution in the industrial and residential areas of Frankfurt is being extended to include vehicle exhaust gases, after experience with sulphur dioxide monitoring. On the basis of meteorogical and pollution measurements made over several years, pollution data and data on the exposure of inhabitants of the area under survey to pollution will be determined by using estimated atmospheric spread patterns.

The substances measured are: SO_2, CO, NO_x, *oxidising agents, total dust, lead and other metals in the dust.*

By investigating the correlation between different pollutants it is possible to optimise the number of measuring points and also the number of elements to be examined; the conditions governing the following items to be examined, must be considered: Area - and time - related pollution levels, patterns of different pollutants, smog warning, the optimising of monitoring networks, and data for epidemiological investigation.

This type of data will produce results which also make it possible to draw up a balance sheet of pollution and anti-pollution factors in densely populated areas.

1. Lage der Meßstellen und Datenverarbeitung

Die bereits 1966 errichtete, seit dem 1.1.1974 in die Bundesstelle für Umweltangelegenheiten ("Umweltbundesamt") integrierte "Probemeßstation Frankfurt/M - Pilotstation für Luftreinhaltung" besteht z.Z. aus einer Zentralstation und sieben Unterstationen (Abb. 1).

Die Zentralstation liegt ca. 1,5 km von der Stadtmitte entfernt in einer Wohn- und Bürogegend. In ca. 6 km Entfernung von der Zentralstation befinden sich an der Peripherie des eigentlichen Frankfurter Stadtkernes die beiden größeren Unterstationen (Ost- und Weststation) mit drei (SO_2, CO, CO_2) bzw. zwei (SO_2, CO_2) Meßkomponenten. Die vier kleineren Unterstationen mit nur einer Meßkomponente (SO_2) sind am Rande des Frankfurter Verdichtungsgebietes und meist außerhalb besiedelter Gebiete errichtet. Zur Überwachung der kfz-spezifischen Komponenten CO, NO, NO_2, O_3 und Blei wurde eine Station in der Frankfurter City eingerichtet. Alle Meßstellen sind über eine Fernwirkanlage und ständig durchgeschaltete Datenleitungen der Deutschen Bundespost mit dem Prozeßrechner der Zentralstation verbunden. Die Fernwirkanlage arbeitet nach dem Frequenzmultiplexverfahren, hierbei können bis zu 18 Meßgeber an eine Leitung angeschlossen werden. Dieses Verfahren ermöglicht eine Mehrfachausnutzung der einzelnen Leitungen.

An der Zentralstation werden die meteorologischen Parameter Windrichtung, Windgeschwindigkeit, relative Feuchte, Luftdruck, Temperatur und Strahlungsbilanz, sowie die Spurenstoffkomponenten Kohlendioxid, Schwefeldioxid, nitrose Gase, Kohlenmonoxid, Gesamt-Kohlenwasserstoffe und Schwebstaubgehalt gemessen. Zur Vermeidung größerer Totzeiten und um Absorptionsverluste in den Leitungen auszuschließen, sind sämtliche Geräte zur

Messung der Spurenstoffe an eine Ringleitung angeschlossen, die mit 1,5 m^3/min belüftet wird. Jedes Gerät wird dann nochmals durch eine eigene Pumpe mit der zur Analyse nötigen Luftmenge versorgt. Die anfallenden Meßwerte werden über Zwischenverstärker generell in eingeprägten Strom von 0 - 20 mA umgesetzt, auf einem Kontrollschreiber kontinuierlich registriert und über einen Bemessungswiderstand an den Eingang des Analog-Digitalwandlers (0 - 1 V) angepaßt. Die von den Außenstellen zur Zentralstation übermittelten Meßwerte werden ebenfalls von der gepulsten Frequenz (2 - 12 Hertz) in eingeprägten Strom umgesetzt und parallel zur Rechnereingabe auf einem Analogschrieb registriert. Auf diese Weise ist eine optimale Kontrolle der Außenstellen von der Zentralstation aus möglich. Analog-Digital-Vergleiche werden im Stichprobenverfahren für alle Komponenten durchgeführt.

Alle 23 Stunden werden die Meßgeräte durch Rechneransteuerung dynamisch geeicht. Durch einen rechnerseitig gesetzten Schließer werden über Relais und Magnetventile zunächst die unteren Eichwerte (Eichgase für CO und CO_2, Nullpatrone für SO_2) aufgegeben: nach 6 Minuten erfolgt durch einen zweiten Schließer die Beaufschlagung der Geräte mit einem oberen Eichwert für ebenfalls 6 Minuten. Aus den Eichwerten (z.B. 300 und 600 ppm), die für jede Meßstelle im Rechner gespeichert sind und aus den diesen Eichwerten entsprechenden Spannungen (z.B. 0,1 und 0,7 Volt), ermittelt der Computer eine Eichgerade, die für die nächsten 23 Stunden gültig ist.

Einen generellen Überblick über die Systematik der vom Prozeßrechner gesteuerten Immissionsmeßstation ist in Abb. 2 gegeben. Die Gesamtrechenanlage besteht aus dem Rechner 60 - 10 der Fa. AEG mit 16 K - Worten Kernspeicherinhalt, dem Verkehrsverteiler und Analog-Digitalwandler mit z.Zt. 48 Eingängen. Zur Zentraleinheit des Rechners kommen zwei Schreibmaschinen (Teleprinter), zwei Lochstreifenstanzer, ein Lochstreifenleser und eine Großrechnerkompatible Magnetband-Einheit hinzu. Auf der ersten Schreibmaschine erfolgt die Ausgabe des Routineprogrammes mit Zeilenkennung, Datum (Jahrestag), Uhrzeit, Halbstundenmittelwerte, Varianzen und 3 Minuten-Maxima. Die zweite Schreibmaschine dient der Korrespondenz mit dem Rechner (Gestörtsetzen einer Meßstelle, Eintragen neuer Eichwerte usw.), der Ausgabe von Störmeldungen durch den Rechner (z.B. Leitungsausfall, Überschreitung eines unteren oder oberen Grenzwertes usw.) und der Protokollierung von Sonderprogrammen. Nach der Ausgabe der Protokolle auf den Schreibmaschinen erfolgt die gleiche Ausgabe unter Wegfall der Blanks auf Stanzer und Magnetband. Die Lochstreifen und Magnetbänder werden auf dem Großrechner des Deutschen Wetterdienstes (CDC 3 400) weiter verarbeitet.

Im einzelnen nimmt der Prozeßrechner folgende Aufgaben wahr:

1. Umsetzung der Analog- in Digitalwerte ·
2. Prüfung dieser Digitalwerte auf Richtigkeit (es kommen hier 5 Kriterien zur Anwendung, wie z.B. Prüfung ob die Anzahl der Einzelwerte für einen statistisch gesicherten Mittelwert ausreicht).
3. Verarbeitung der geprüften Einzelwerte zu statistischen Kenngrößen.
4. Automatische Eichung der Meßgeräte.

Durch die Punkte 1 - 4 ist eine optimale Sicherstellung der Richtigkeit der auf den Lochstreifen ausgegebenen Meßwerte gegeben. Nachträgliche und zeitraubende Korrekturen werden auf ein Mindestmaß beschränkt.

In der Routineverarbeitung werden z.Zt. die Häufigkeitsverteilungen und mittleren täglichen Gänge aller Komponenten für jeden Monat oder beliebig wählbare Zeiträume errechnet. Für Sonderauswertungen und den Nachtrag von Meßkollektiven, der z.T. durch Leitungs- oder Rechnerausfall bei Wartungsarbeiten notwendig wird, steht ein Tischrechner der Firma Hewlett Packard Typ 9810 A mit 2036 Programmschritten und 111 Datenregistern zur Verfügung. Diesem Tischrechner sind als periphere Einheit ein Lochstreifenleser, ein Plotter und ein Teleprinter mit Stanzer angeschlossen. Eine umfangreiche Anzahl von festverdrahteten Funktionen für mathematische und statistische Zwecke, sowie für die Plotter-Programmierung ermöglichen eine leichte Weiterverarbeitung der angefallenen Meßwerte. Im Sinne einer Zeitersparnis wird damit auch die Eingabe eines nach speziellen Gesichtspunkten vom Großrechner erstellten Lochstreifens in den Tischrechner sinnvoll.

2. Lage und Instrumentierung der Mehrkomponenten-Meßstation zur Überwachung und Analyse der Immissionen von Kraftfahrzeugabgasen in der Frankfurter City.

Zur Messung der durch Kraftfahrzeugverkehr verursachten Immissionen in der City Frankfurts wurde im Juli 1972 in der Frankfurter Innenstadt zwischen Hauptwache und dem Eschenheimer Turm eine Mehrkomponenten-Meßstelle eingerichtet (Abb. 1). Die im weiteren als City-Station Rundschauhaus bezeichnete Meßstelle liegt an einer dreispurig befahrenen Hauptstraße mit hoher Verkehrsfrequenz. Die Analysengeräte sind in 5 und in 20 m Höhe in im Freien stehenden Meßschränken untergebracht.

Die Ansaugstelle ist 40 m von der nächsten Straßenkreuzung entfernt und befindet sich in der Mitte des Bürgersteiges 3,5 m über Straßengrund bzw. 3,5 Meter Dachhöhe (ca. 23 m über Straßengrund).

An der Meßstelle wird der Verkehr durch Einbahnregelung in südnördlicher Richtung geführt. Die Verkehrsfrequenz ist in den Tagesstunden ständig sehr stark (ca. 1300 Kfz/Stunde) und erreicht in den Nachmittags- und Abendstunden ihr absolutes Maximum (ca. 2000 Kfz/h). Zur Zeit der abendlichen "rush-hour" wird die Straße, bedingt durch Ampelsteuerung und Verkehrsaufkommen, bis an die Grenze ihrer Aufnahmefähigkeit belastet. Die Bebauung ist in der Nähe der Meßstelle

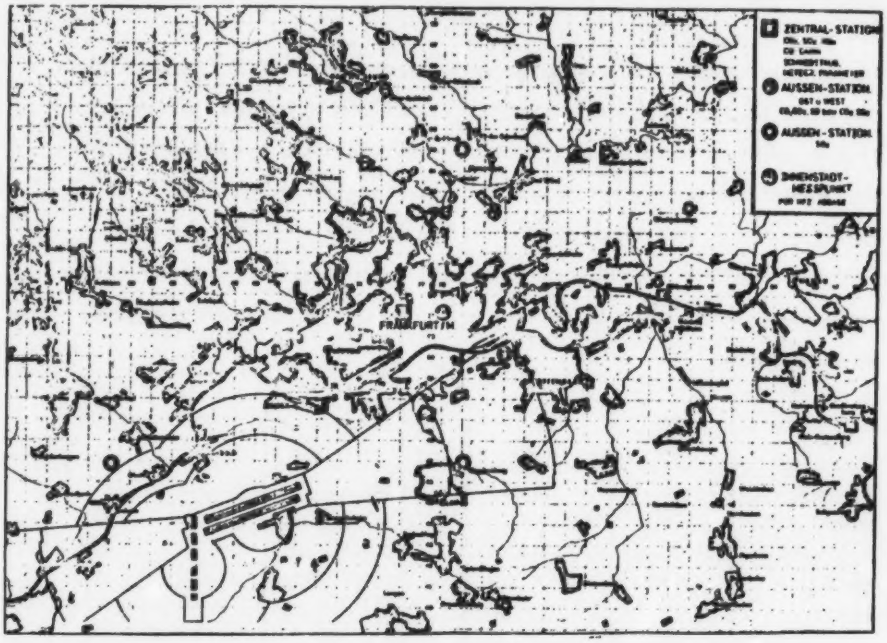

ZENTRAL-STATION
AUSSEN-STATION
OST u. WEST
AUSSEN-STATION
INNENSTADT-MESSPUNKT
FRANKFURT/M

Abbildung 1

Blockschaltbild der automatisierten Immissions-Meßstation Frankfurt/M.

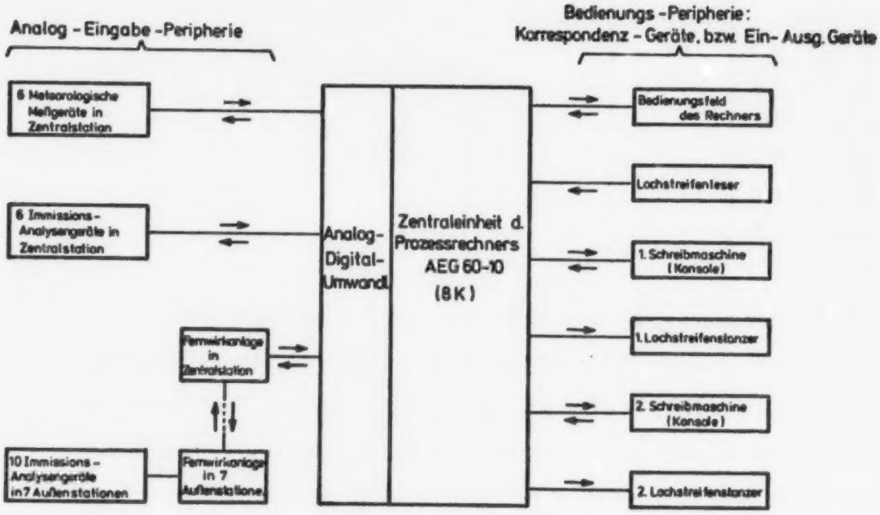

Analog - Eingabe -Peripherie
Bedienungs -Peripherie:
Korrespondenz - Geräte, bzw. Ein- Ausg. Geräte
6 Meteorologische Meßgeräte in Zentralstation
6 Immissions - Analysengeräte in Zentralstation
Fernwirkanlage in Zentralstation
10 Immissions - Analysengeräte in 7 Außenstationen
Fernwirkanlage in 7 Außenstationen
Analog-Digital-Umwandl.
Zentraleinheit d. Prozessrechners AEG 60-10 (8K)
Bedienungsfeld des Rechners
Lochstreifenleser
1. Schreibmaschine (Konsole)
1. Lochstreifenstanzer
2. Schreibmaschine (Konsole)
2. Lochstreifenstanzer

Abbildung 2

geschlossen und einheitlich ca. 20 m hoch.

Im Moment erfolgt die Messung von Kohlenmonoxid (CO), Stickstoffmonoxid (NO), Stickstoffdioxid (NO_2) und Ozon in beiden Ebenen mittels kontinuierlicher Infrarot- und Chemoluminiszenz-Verfahren. In der ersten Etage werden zusätzlich Filterproben (low volume) zur Analyse der Schwermetallkonzentrationen (Blei, Eisen, Kupfer, Cadmium) mittels Atomabsorptionsspektrometrie gezogen. Analysenmethoden, Gerätetyp und Herstellerfimra sind der folgenden Tabelle zu entnehmen:

	CO	NO	NO_2	O_3	Schwermetalle
1. Etage: Ansaughöhe 3.5 m über Straßengrund	Infra-Rot Uras II Hartmann + Braun	Chemoluminiszenz NO_x-Monitor Bendix	wie NO	Chemoluminiszenz Ozon-Monitor Bendix	Filterproben mit low volume bei 24 Stunden Sammeldauer Atomabsorptionsspektrometrie Perkin+Elmer
Dach Ansaughöhe 3.5 m über Bebauungshöhe und ca. 23 m über Straßengrund	wie 1. Etage	wie 1. Etage	wie 1. Etage	wie 1. Etage	entfällt

Die Unterbringung der Meßgeräte im Freien ermöglicht relativ kurze Ansaugleitungen und gute Wartungsbedingungen, die insbesondere die Ozon- und NO_x-Messung wesentlich erleichtern. Der Einfluß der schwankenden Außentemperaturen und der Aufheizung der Meßschränke durch Sonneneinstrahlung konnte durch eingebaute Lüfter innerhalb der werksseitig angegebenen Toleranzgrenzen für die einzelnen Meßgeräte gehalten werden.

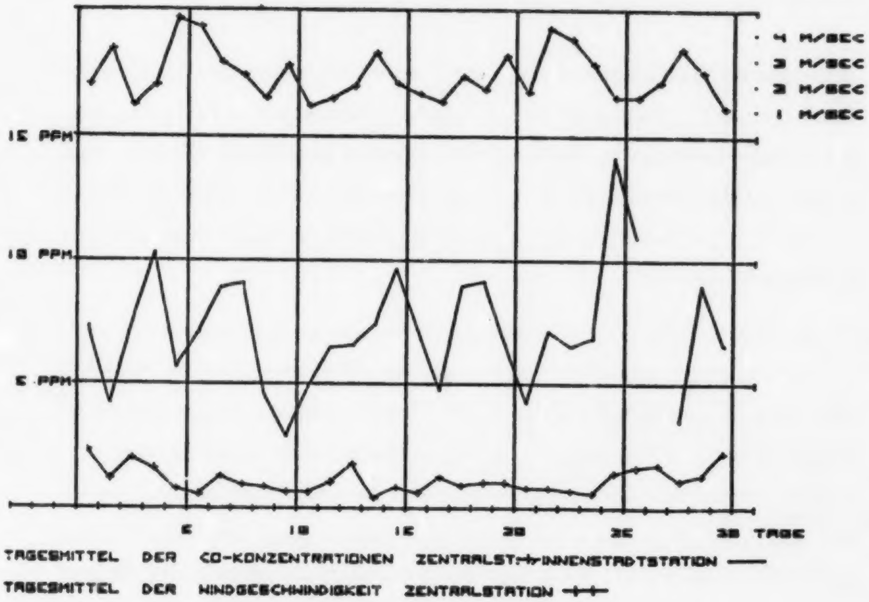


Abb. 3. Pilotstation des BMI Frankfurt/Main - Juni 1973.

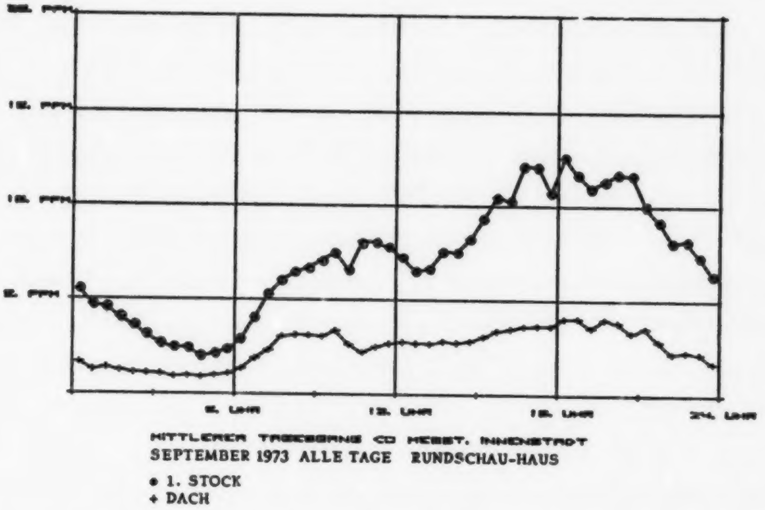


Abb. 4. Pilotstation für Luftreinhaltung.

3. Das horizontale und vertikale CO - Konzentrationsfeld.

Während bei der Überwachung der Schwefeldioxidkonzentrationen in Gebieten, die vorwiegend durch Hausbrandemission beeinflußt sind, ein relativ homogenes Konzentrationsfeld angenommen werden kann, treten bei den durch Kraftfahrzeugemissionen verursachten Immissionen in der Straßenluft starke horizontale und vertikale Konzentrationsgradienten auf.

So beträgt der Unterschied zwischen den an der Zentralstation und den in der City gemessenen mittleren SO_2-Konzentrationen ungefähr 25%. Die CO-Konzentrationen an der Zentralstation liegen jedoch oft um den Faktor 10 niedriger als die in der Innenstadt im Straßenniveau ermittelten CO-Konzentrationen. In Abb. 3 ist beispielhaft der Verlauf der Tagesmittelwerte an diesen beiden Stationen für den Juni 1973 dargestellt. Es zeigen sich deutlich die oben beschriebenen Konzentrationsunterschiede, wobei außerdem nur eine schwache Korrelation zwischen den Einzelwerten besteht.

In Abb. 4 sind für den Monat September 1973 die mittleren täglichen CO-Konzentrationsvariationen dargestellt, für die Meßhöhen 3.50 m und 23 m über Straßenniveau, die bestätigen, daß auch in den City-Bereichen der Großstädte die von Kraftfahrzeugen emittierten Primäremissionen sehr schnell mit der Höhe abnehmen. Nach Untersuchungen in Berlin (Lahmann, 1972) und Frankfurt (Busch, Georgii, Weber, 1967) kann die CO-Abnahme mit der Höhe in Strassenschluchten expontiell angesetzt werden, wobei wegen des "Streetcanyoneffekts", d.h. der Ausbildung einer rotorartigen Strömung bei Windrichtungen quer zur Bebauungsflucht, noch eine starke Abhängigkeit der CO-Konzentrationen von der Windrichtung zu beobachten ist. Abb. 5 zeigt, daß eine Winddrehung um 180° die gleiche Konzentrationserhöhung bzw. -erniedrigung bewirken kann, wie eine Steigerung der Windgeschwindigkeit von 0.5 auf 4.5 m/sec.

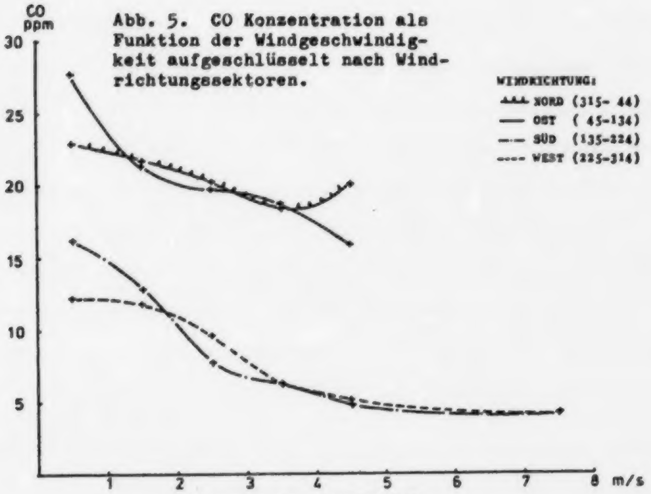
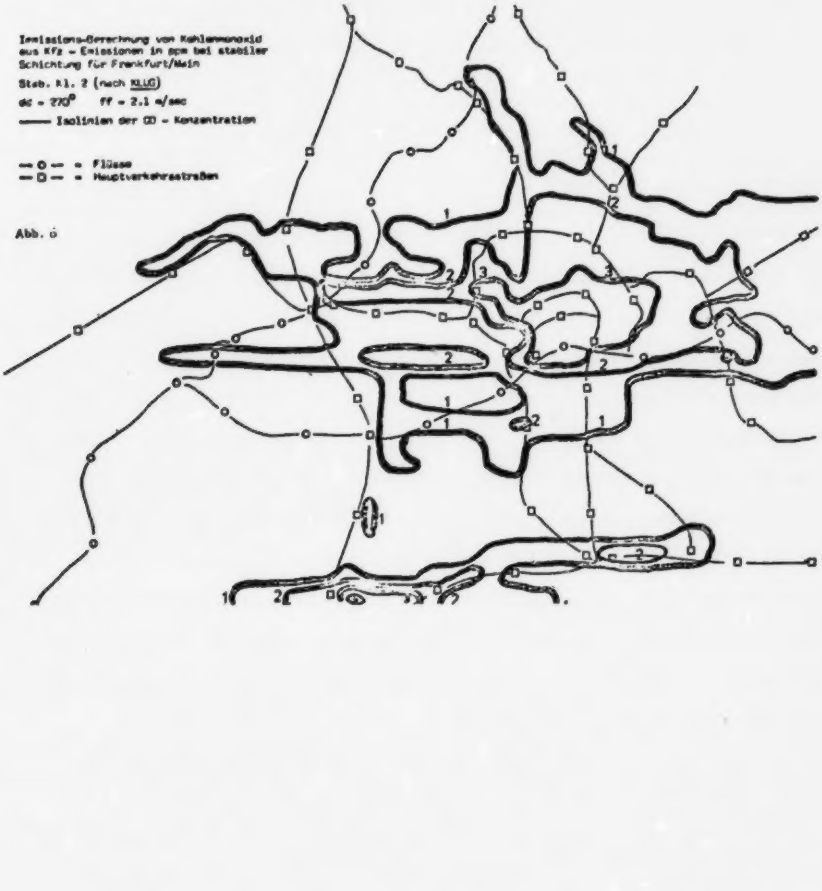


Abb. 5. CO Konzentration als Funktion der Windgeschwindigkeit aufgeschlüsselt nach Windrichtungssektoren.

CO RUNDSCHAU-HAUS WINTER 1972



Immissions-Berechnung von Kohlenmonoxid aus Kfz - Emissionen in ppm bei stabiler Schichtung für Frankfurt/Main

Stab. Kl. 2 (nach KLUG)

dd = 270° ff = 2.1 m/sec

—— Isolinien der CO - Konzentration

—○— = Flüsse
—□— = Hauptverkehrsstraßen

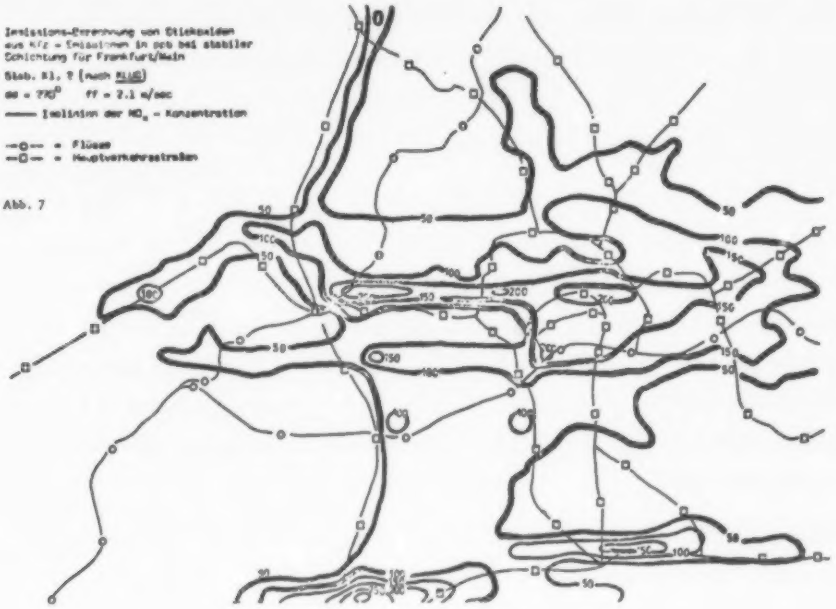
Abb. 6

Die starken vertikalen und horizontalen CO-Konzentrationsunterschiede im Stadtgebiet, denen durch die Variation der Emission und der Ausbreitungsparameter im Tages- und Jahresverlauf noch ein zeitlicher Gang überlagert ist, machen eine örtlich und zeitlich repräsentative Immissionsbestimmung äußerst schwierig. In Frankfurt wird zur Lösung dieser Frage versucht, die im Stadtgebiet vorkommenden oder auch augenblicklich herrschenden CO-Konzentrationen nach unten und oben abzugrenzen. In der Umgebung der City Station können, bedingt durch Verkehrsaufkommen und Bebauung die maximalen CO-Belastungen sehr gut erfaßt werden.

An der Zentralstation werden für Büro-und Wohngegenden repräsentative Konzentrationen erfaßt. Damit ist sichergestellt, daß die Einwohner Frankfurts meistens Konzentrationen ausgesetzt sind die zwischen den an diesen beiden Stationen gemessenen Werten liegen.

4. Modellierung des CO - Konzentrationsfeldes.

Zur Unterstützung der meßtechnischen Erfassung der CO-Konzentrationen wird z.Z. in Frankfurt versucht, die durch Kraftfahrzeuge verursachten Luftverunreinigungen durch Modellrechnungen abzuschätzen. Ausgehend von Verkehrsmengenzahlen und mittleren Geschwindigkeiten in Rastern von 500 x 500 m konnte mit Hilfe von Emissionsfaktoren die mittlere tägliche CO-Emission pro Einheitsfläche errechnet werden. Diesen Emissionsfaktoren liegen umfangreiche Untersuchungen in Köln zugrunde (Emissionskataster Köln 1972), bei denen durch Meßfahrten unterschiedliche Fahrzyklen und deren Häufigkeitsverteilung ermittelt werden konnten. Korrelationsrechnungen zeigten, daß jeder Zyklus in guter Näherung durch die mittlere Zyklusgeschwindigkeit definiert ist. Die einzelnen Zyklen wurden durch Prüfstandversuche simuliert und die dabei emittierten Mengen der Kfz-Abgase gemessen.



Immissions-Berechnung von Stickoxiden aus Kfz - Emissionen in ppb bei stabiler Schichtung für Frankfurt/Main

Stab. Kl. 2 (nach KLUG)

dd = 270° ff = 2.1 m/sec

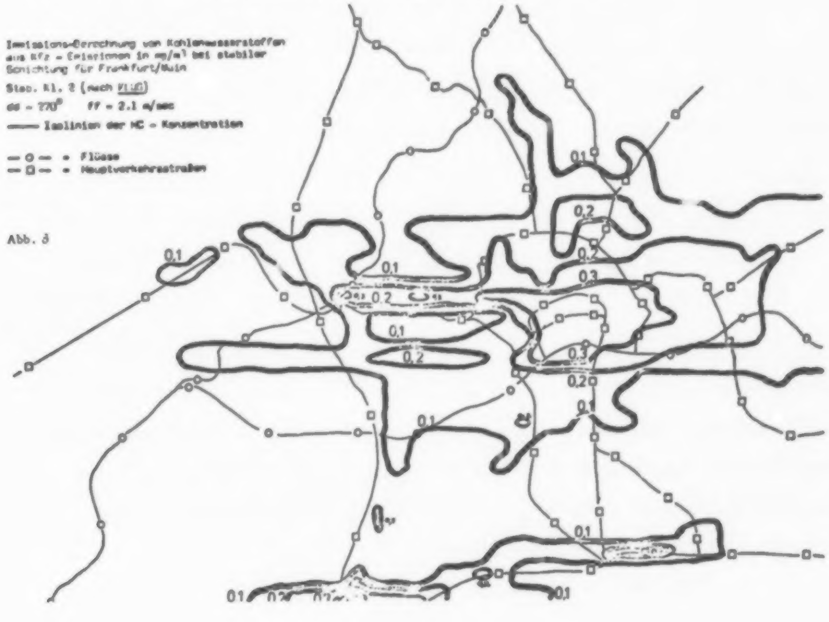
—— Isolinien der NO_x - Konzentration

—○— = Flüsse

—□— = Hauptverkehrsstraßen

Abb. 7

50
100
150
200
50
100
150
100
50



Immissions-Berechnung von Kohlenwasserstoffen aus Kfz - Emissionen in mg/m³ bei stabiler Schichtung für Frankfurt/Main

Stab. Kl. 2 (nach KLUG)

dd = 270° ff = 2.1 m/sec

—— Isolinien der HC - Konzentration

—○— = Flüsse

—□— = Hauptverkehrsstraßen

Abb. 8

0,1
0,2
0,3
0,1
0,2
0,1
0,2
0,3
0,2
0,1
0,1
0,1

Aus den Verkehrsdaten und den Emissionsfaktoren konnten für das Stadtgebiet von Frankfurt folgende Emissionen ermittelt werden:

CO	:	154	Tonnen / Tag
NO	:	7.1	" "
CnHm	:	4.6	" "

Nach Berechnung der Emissionen erfolgte in einem weiteren Schritt mittels eines Diffusionsmodells (Baltrusch 1972) die Berechnung der Immissionskonzentrationen. Dabei wurden die in den Flächen (500 x 500) emittierten Mengen als Punktquelle in der Rastermitte zusammengefaßt und für ein gleichliegendes Immissionsraster durch Superposition der einzelnen "Rauchfahnen" die Schadgaskonzentrationen errechnet.

Überprüfungen der errechneten Ergebnisse zeigten, daß die zuerst gewählte Dimensionierung von Emissions- und Immissionsraster (jeweils 500 x 500 m) nicht die Bedingungen einer Flächenquelle erfüllte, und daß deshalb zu hohe Konzentrationen errechnet wurden. Erst eine Unterteilung der pro 500 x 500 m Einheitsflächen errechneten Emission auf 25 im jeweiligen Raster gleichverteilte Einzelquellen ermöglichte die Errechnung korrekter Konzentrationen. Die Berechnungen wurden für die vier Hauptwindrichtungen (Nord, Ost, Süd, West) und für unterschiedliche atmosphärische Stabilität durchgeführt.

Das hier beschriebene Modell kann als "städtisches Backgroundmodell" bezeichnet werden, bei dem Emissionen aus den Straßenschluchten herausgehoben und in einer Höhe von 20 Metern als Punktquellen angenommen werden. Für diese Höhe sind auch die später angegebenen Konzentrationswerte berechnet. Die Konzentrationen im Straßenniveau werden auf diese Weise nicht erfaßt und müssen durch ein besonderes Straßenmodell, das in Vorbereitung ist, berechnet werden.

In Abb. 6, 7 und 8 sind für die Stabilitätsklasse 2 (nach Klug) Westwind und für eine mittlere Geschwindigkeit von 2.1 m/sec die Konzentrationsfelder für Kohlenmonoxid (CO), Stickoxide (NO_x) und Kohlen-

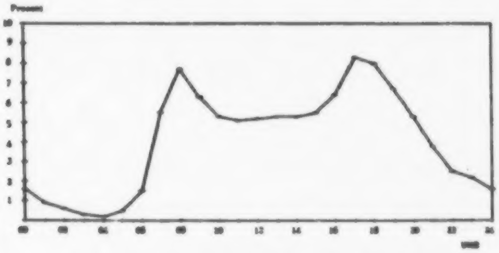


Abb. 9. Prozentuale Verteilung des Tagesverkehrs in Frankfurt/Main.

Abb. 10. Mittlerer Tagesgang Kohlenmonoxid (gemessen am Inst. für Meteorologie u. Geoph.).

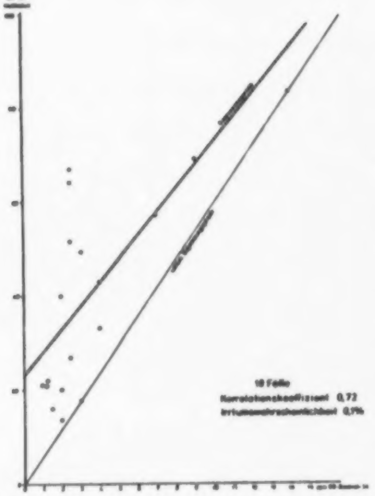


Abb. 11. Korrelation der CO-Werte an der Zentral-Station mit den CO-Werten der Stadtrundfahrten zum 1700 Termin.

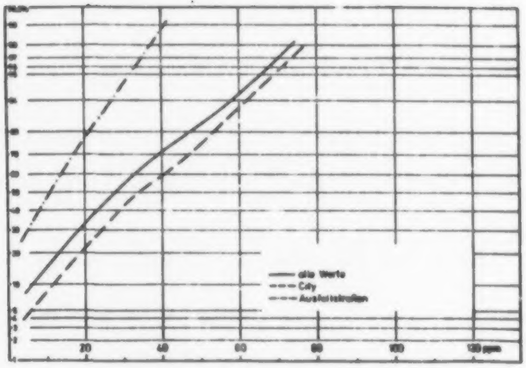


Abb. 12. Summenhäufigkeit der 4min CO Mittelwerte.

wasserstoffe (HC) dargestellt. Die Linien gleicher Konzentration zeigen deutlich den Einfluß der City und des Autobahnkreuzes im Südwesten Frankfurts (Maximalwert 4 ppm CO). Zu bemerken ist, daß die hier errechneten Tagesmittelkonzentrationen gut mit den im Dachniveau der City-Station gemessenen Konzentrationswerten übereinstimmen.

Zur Simulation des Tagesganges der CO-Konzentrationen wurden, gemäß dem Verlauf des Verkehrsaufkommens (Abb. 9), die errechneten Konzentrationen gewichtet und der Tagesgang der atmosphärischen Stabilität überlagert. Durch diese Methode konnte der an der Zentralstation gemessene mittlere tägliche Verlauf der CO-Konzentrationen (Abb. 10) sowohl in der Höhe der Konzentrationswerte als auch in seiner Form gut angenähert werden. Insbesondere die in den Sommermonaten beobachtete Verschiebung des abendlichen CO-Maximums in die späten Abendstunden ergab sich aus dem Gang der Stabilität. Wie Abb. 9 zeigt sinkt das Verkehrsaufkommen von seinem Spitzenwert um 17 Uhr bis 20 Uhr auf die Hälfte ab, sodaß bei konstanten Stabilitätsbedingungen auch die Konzentration auf die Hälfte absinken müßte. Unter der Annahme, daß im Mittel die atmosphärische Stabilität zwischen diesen Zeitpunkten um eine Klasse stabiler wird, ergibt sich eine Erhöhung der Werte um Faktor 3. Dadurch wird das sinkende Verkehrsaufkommen kompensiert und das abendliche CO-Maximum auch rechnerisch um 20 Uhr ermittelt.

5. Mobile Messung der Kohlenmonoxid-Konzentration

Als Ergänzung zur stationären Kohlenmonoxid-Messung, und zur Untersuchung der Belastung des Autofahrers während seines Weges von und zur Arbeitsstelle, wurden 1969 und im Winterhalbjahr 1970/71 CO-Messungen mit einer mobilen Meßstation durchgeführt.

Die Streckenführung während der Meßperiode 1969 erfaßte den westlichen Teil Frankfurts, das Gebiet um den Hauptbahnhof und die City.

Die Messungen wurden von 17.oo bis 17.3o Uhr durchgeführt. In der zweiten Meßperiode (1970/71) wurde jeweils morgens zwischen 7.3o und 9.3o Uhr und abends zwischen 17.oo und 19.oo Uhr ein west-östliches Profil gefahren. Verwendet wurde das Gasspurgerät der Firma Dräger mit Prüfröhrchen "CO - 5 b".

Die Ansaugstelle befand sich jeweils in Höhe des rechten, vorderen Ausstellfensters des verwendeten Kraftfahrzeuges.

Eine Korrelationsrechnung der durch mobile Messungen ermittelten Kohlenmonoxid-Konzentrationen mit den an der Zentralstation gemessenen CO-Werten während der ersten Meßperiode (1969) ergab einen Korrelationskoeffizienten von 0.72 (Abb. 11), für die Winterhalbjahre 1970-71 lag der Korrelationskoeffizient bei 0.6. Daraus ergibt sich für beide Untersuchungen ein signifikanter, statistischer Zusammenhang der Meßwertkollektive, der wesentlich durch den täglichen Gang von Verkehrsaufkommen und CO-Konzentration bestimmt wird. Die Abweichungen der Einzelwerte von den Regressionsgeraden sind aber so groß, daß für den Einzelfall die CO-Konzentrationen in der Innenstadt nicht aus den an der Zentralstation gemessenen CO-Konzentrationen ableitbar sind. So treten z.B. 1969 bei CO-Konzentrationen zwischen 2 und 3 ppm an der Zentralstation in der Innenstadt im fließenden Verkehr CO-Konzentrationen zwischen 17 und 70 ppm auf.

Für die CO-Messungen in der Winterperiode 1970/71 wurden die ermittelten Werte nach Tageszeit (morgens bzw. abends) und Stadtbezirk (Ausfallstraßen, Außenbezirke, Stadtzentrum) getrennt untersucht.

Die Darstellung der Meßwerte in Form von Summenhäufigkeitsverteilungen (Abb. 12) ergibt folgende 50%-Werte:

für das gesamte Wertekollektiv	38 ppm
Konzentration auf den Ausfallstraßen	14 ppm
Konzentration im Citybereich	44 ppm

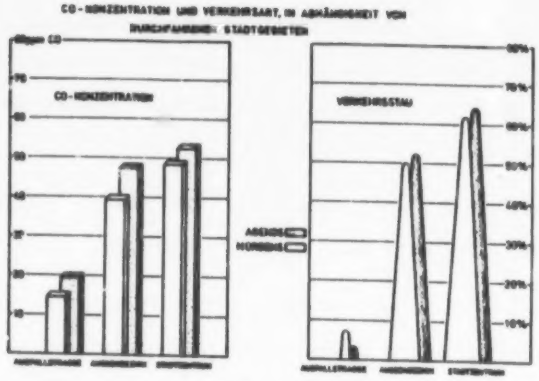

CO-KONZENTRATION UND VERKEHRSART, IN ABHÄNGIGKEIT VON
DURCHFAHRENEN STADTGEBIETEN
80ppm CO
70
60
50
40
30
20
10
CO-KONZENTRATION
ABENDS
MORGENS
VERKEHRSSTAU
80%
70%
60%
50%
40%
30%
20%
10%

Abb. 13

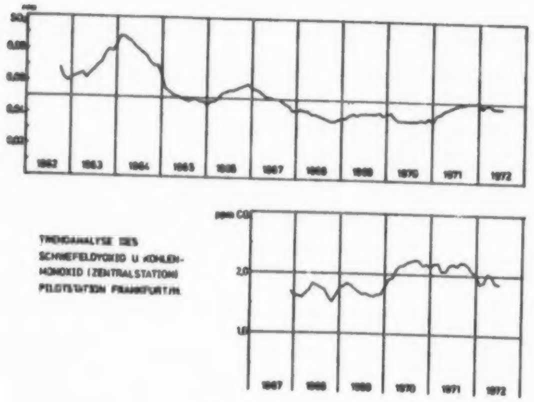

0,10
0,08
0,06
0,04
0,02
1962
1963
1964
1965
1966
1967
1968
1969
1970
1971
1972
TRENDANALYSE DES
SCHWEFELDYOXID U KOHLEN-
MONOXID (ZENTRALSTATION)
PILOTSTATION FRANKFURT/M.
ppm CO
2,0
1,0
1967
1968
1969
1970
1971
1972

Abb. 14

Die Trennung der Meßwerte nach den durchfahrenen Stadtbereichen in Ausfallstraße, Außenbezirk und Stadtzentrum sowie nach morgens und abends ergibt die in Abb. 13 dargestellten CO-Konzentrationswerte. Abb. 13 zeigt, daß die 3 Bereiche (Ausfallstraße, Außenbezirk, Stadtzentrum) im Mittel deutliche Unterschiede der CO-Konzentration und der Fahrtanteile mit Verkehrsstau aufweisen (rechte Seite der Abbildung). Die höchsten Konzentrationen wurden abends im Stadtzentrum gemessen. Der arithmetische Mittelwert aus 20 Einzelwerten ergab 52 ppm. Die Konzentrationen der anderen Stadtgebiete sind der Abb. 13 zu entnehmen.

6. Trendanalyse der CO - Konzentrationen.

Neben den bereits beschriebenen mittleren täglichen Konzentrationsvariationen und den Summenhäufigkeitsverteilungen ist die Trendanalyse eine weitere wichtige Hilfsgröße bei der Beurteilung der Entwicklung der Luftverunreinigung. Auch hier ergeben sich, gerade bei der Anwendung dieser Methoden auf die durch Kraftfahrzeuge emittierten Komponenten, große Interpretationsschwierigkeiten, weil der Trendverlauf sowohl durch eine großräumige Entwicklung (z.B. Erhöhung des allgemeinen Verkehrsaufkommens, Erniedrigung der Emissionen durch technologische Maßnahmen) als auch durch Änderungen der Verkehrsführung in unmittelbarer Nähe der Meßstelle verursacht werden kann. Die in Abb. 14 dargestellte Trendanalyse für die Schwefeldioxid- und Kohlenmonoxid-Konzentrationen, gemessen an der Zentralstation, zeigt ein deutliches Absinken der SO_2-Konzentrationen im Verlauf der Meßperiode, während die Kohlenmonoxid-Konzentrationen zwischen 1969 und 1970 einen deutlichen Trend zu höheren Werten zeigen. Es kann zwar angenommen werden, daß diese Erhöhung eine Folge der steigenden Zulassungszahlen der Kraftfahrzeuge ist, doch ist der Absolut-Wert der Änderung so gering, daß wegen der Meßungenauigkeit eine gesicherte Aussage nicht möglich ist.

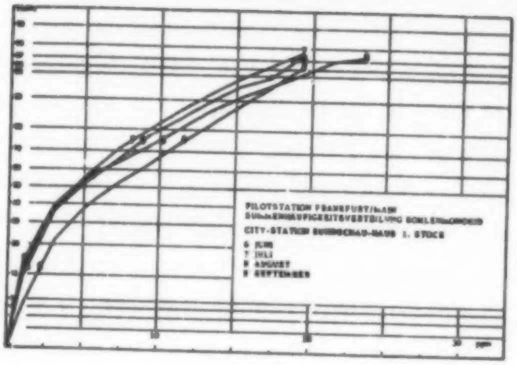


Abb. 15

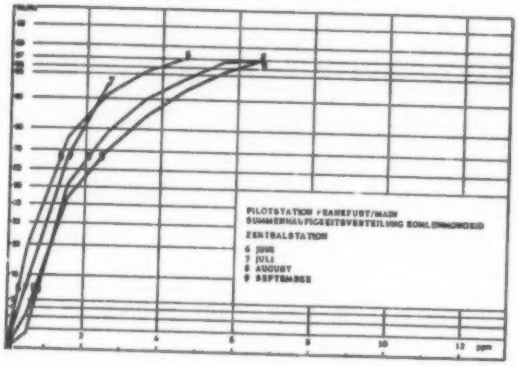


Abb. 16

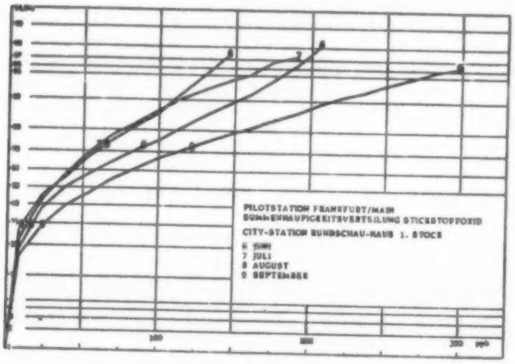


Abb. 17

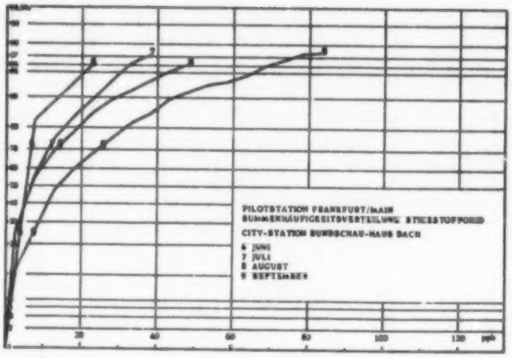


Abb. 18

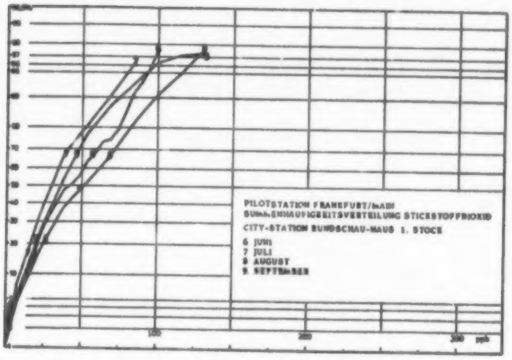


Abb. 19

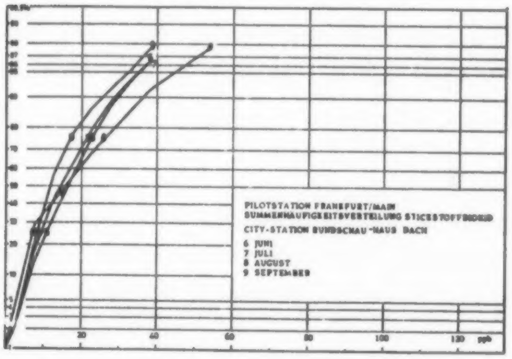


Abb. 20

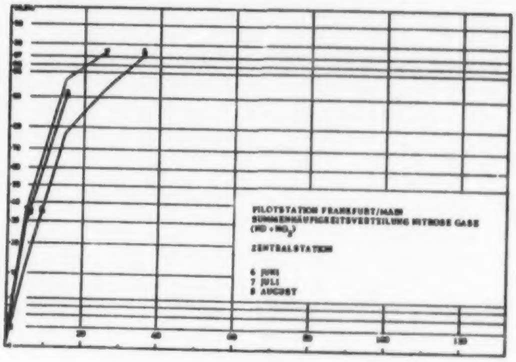


Abb. 21

7. Kohlenmonoxid als Leitsubstanz für die Überwachung von Kraftfahrzeug-Emissionen.

Die in Kap. 3 in der Form der mittleren täglichen Konzentrationsvariationen beschriebene Abnahme der kdurch Kraftfahrzeuge verursachten CO-Immissionen mit der Höhe und dem Abstand zur City gilt in gleicher Weise für die Immissionen nitroser Gase. Zur Verdeutlichung dieses Sachverhaltes sind aus den Darstellungen der Summenhäufigkeitsverteilungen für die Meßorte "City-Station 1. Stock", "City-Station Dach" und "Zentralstation" für die Komponenten CO, NO und NO_2 bzw. NO_x (Abb. 15 bis 21) die 50 und 97.5 Perzentile in Tab. 1 zusammengestellt.

Bei der Beurteilung dieser Werte ist zu beachten, daß diesen Auswertungen die Gesamtkollektive, also auch die niedrigen Nachtwerte, zugrunde liegen. Dadurch werden insbesondere die 50%-Werte stark herabgesetzt.

Somit bestätigt sich die eingangs gemachte Feststellung, daß sich die für die CO-Konzentrationen ermittelten Unterschiede zwischen den einzelnen Stationen in den Konzentrationen der Stickoxide wiederholen.

Dies bestätigt zunächst, daß das Kohlenmonoxid als Leitsubstanz für

TAB 1

	Monat	City Station 1. Stock 50%	City Station 1. Stock 97.5%	City Station Dach 50%	City Station Dach 97.5%	Zentralstation 50%	Zentralstation 97.5%
C O	Juni	4.9	19			1	4.4
	Juli	4.5	19.5			1.2	2.9
	August	7	21			1.4	7.0
	September	5	23			1.7	7.0
N O	Juni	23	145	6	28		
	Juli	28	190	7	40		
	August	40	200	7	53		
	September	60	320	13	83		
NO_2	Juni	42	100	17	43		
	Juli	30	90	15	43		
	August	51	130	16	54		
	September	34	135	12	38		
NO_x	Juni					10	38
	Juli					6	30
	August					7	--
	September					--	--

die ebenfalls durch die Kraftfahrzeuge emittierten Nitrosen Gase gelten kann. Betrachtet man die in Abb. 22 dargestellten mittleren täglichen Konzentrationsvariationen der Komponenten CO, NO, NO_2, gemessen an der "City-Station 1. Stock" im Juli 1973 so zeigt sich allerdings eine deutliche Abweichung im Verlauf der NO- und CO-Konzentrationen. So ist der der morgendlichen "rush-hour" entsprechende Konzentrationspeak beim NO deutlich beim CO dagegen gar nicht ausgeprägt und erst gegen 11.oo Uhr ist zwischen CO und NO ein weitgehend paralleler Verlauf zu beobachten. Umgekehrt dazu ist der Zusammenhang zwischen CO und NO_2 in den Morgenstunden relativ gut, in den Nachmittagsstunden dagegen schlechter ausgeprägt.

Qualitativ können diese Unterschiede zwischen NO und CO durch die unterschiedlichen Emissionsverhältnisse im Abgas erklärt werden, die eine Funktion des Fahrzyklus bzw. der mittleren Fahrgeschwindigkeit sind. Für das Konzentrationsverhalten der Komponenten CO und NO_2 sind in den Sommermonaten photochemische Prozesse maßgebend, die je nach Einstrahlung unterschiedliche Verhältniswerte verursachen.

Aus diesen Untersuchungen folgt, daß das Kohlenmonoxid zwar für viele Problemstellungen als Leitsubstanz bei der Überwachung der Kfz-Abgase dienen kann, für spezielle Untersuchungen, z.B. für photochemische Prozesse, müssen allerdings die relevanten Komponenten mitanalysiert werden.

8. Abschätzung des CO - Dosisangebots

Wie in den vorhergehenden Kapiteln beschrieben, liegen für Frankfurt für den City-Bereich und den Wohnbereich kontinuierliche Meßreihen der Kohlenmonoxidkonzentrationen vor, die durch mobile Messungen und Modellrechnungen vervollständigt werden. Mit diesem Datenmaterial läßt sich das Dosisangebot abschätzen, das als zeitli-

TABELLE II

		Fahrt zur Arbeitsst.	Arbeitsplatz	Fahrt zur Wohnung		Fahrt zur Arbeitsst.	Arbeitsplatz	Fahrt zur Wohnung
1a.	mittl.Konz.	40 ppm	8 ppm	40 ppm	**2.**	40 ppm	1,5 ppm	40 ppm
	Exposit. Dauer	30 min	9 Std.	30 min		30 min	9 Std.	30 min
	Dosis-angebot	20 ppm x Std.	72 ppm x Std.	20 ppm x Std.		20 ppm x Std.	15,5ppm x Std.	20 ppm x Std.
	Anteil an d.Gesamt-dosis	18 %	64 %	18 %		37 %	26 %	37 %
1b.	mittl.Konz.	40 ppm	4 ppm	40 ppm	**3.**	2 ppm	1,5 ppm	2 ppm
	Exposit. Dauer	30 min	9 Std.	30 min		30 min	9 Std.	30 min
	Dosis-angebot	20 ppm x Std.	36 ppm x Std.	20 ppm x Std.		1 ppm x Std.	13,5ppm x Std.	1 ppm x Std.
	Anteil an der Gesamt-dosis	26 %	48 %	26 %		6,5 %	87 %	6,5 %

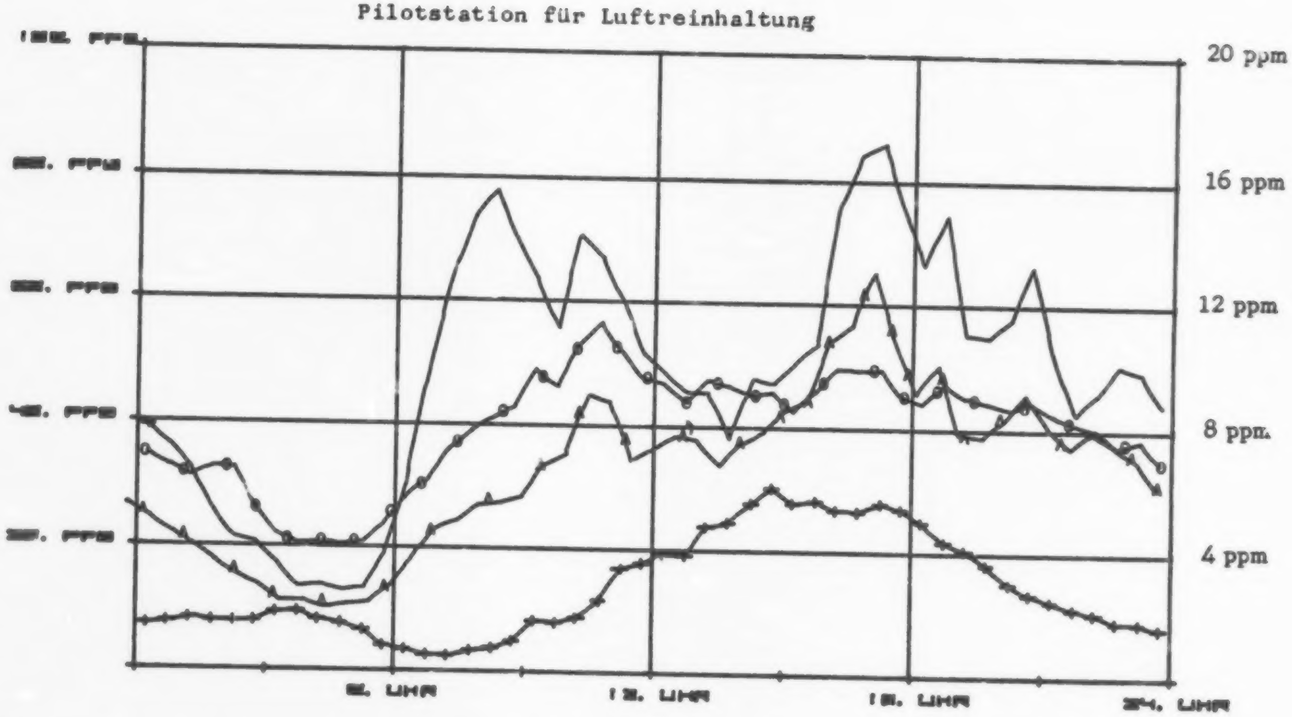


Abb. 22

Mittlerer Tagesgang CO, NO, NO_2, O_3

Rundschau-Haus 1. Stock Juli 1973

ches Integral über die Konzentration definiert ist. Bei dieser Abschätzung tritt zu dem Problem der zeitlichen und örtlichen Varianz der Kohlenmonoxid-Konzentrationen die Schwierigkeit hinzu, die Aufenthaltsdauer von Personengruppen in den unterschiedlichen Konzentrationsniveaus zu bestimmen.

Im augenblicklichen Stand ist es nur möglich, Grenzfälle für maximale und minimale Expositionen im Stadtgebiet anzugeben. Folgende drei Fälle werden betrachtet:

1. Berufstätiger Pendler mit Arbeitsplatz im City-Bereich. Der Arbeitsplatz ist
   a) im Straßenniveau
   b) in ca. 20 Metern Höhe
   Die Fahrzeit von und zur Arbeitsstelle beträgt jeweils eine halbe, die Arbeitszeit selbst 9 Stunden.
2. Berufstätiger Pendler wie unter 1. mit Arbeitsplatz in einer Büro- und Wohngegend.
3. Berufstätiger der auf seinem Weg zur Arbeit nur Wohngegenden passiert und auch in einer Büro- und Wohngegend arbeitet.

Für jeweils zehn Stunden Aufenthalt im Stadtgebiet von 7 - 17 Uhr ergibt sich für die Fälle 1 - 3 die in Tab. 2 dargestellte Belastung.

Bei diesen Schätzungen wurde von mittleren Sommerkonzentrationen ausgegangen, weil in dieser Jahreszeit die CO-Immission in Frankfurt/M fast ausschließlich durch den Kraftfahrzeugverkehr verursacht wird. Im Winter liegen die CO-Konzentrationen durch Feuerungsemissionen und größere atmosphärische Stabilität höher. In einzelnen Fällen, d.h. an Tagen mit austauscharmen Wetterlagen können die Mittelkonzentrationen über 8 Stunden bei 30 ppm liegen, auch dieser Fall ist hier nicht berücksichtigt.

Unter den in 7. genannten Einschränkungen lassen sich mittels der bekannten Emissionsverhältnisse im Kraftfahrzeugabgas (Emissionskataster Köln) diese Abschätzungen auf die Nitrosen Gase und Kohlenwasserstoffe übertragen.

Literaturverzeichnis

LAHMANN, E., 1972 — CO Concentrations in the Urban Area of Berlin, VDI Berichte, Band 180, S. 40 - 45

GEORGII, H.W., 1968
BUSCH, E.
WEBER, E. — Untersuchungen über die zeitliche und räumliche Verteilung der Immissionskonzentration des Kohlenmonoxid in Frankfurt a.M., Ber. Nr. 11 Inst. f. Meteorologie und Geophysik der Universität Frankfurt a.M.

EMISSIONSKATASTER 1972
Köln — Minister für Arbeit, Gesundheit und Soziales des Landes Nordrhein-Westfalen

BALTRUSCH, M., 1972 — Dreidimensionale Analyse des CO-Konzentrationsfeldes über einer Flächenquelle. Diplomarbeit, Institut für Meteorologie und Geophysik der Universität Frankfurt a.M.

INCORPORATION OF POPULATION EXPOSURE CONCEPTS IN AIR QUALITY CRITERIA DOCUMENTS

ARTHUR C. STERN AND YUJI HORIE

Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina at Chapel Hill, USA

ABSTRACT

Short, intermediate and long term responses of human, vegetation, animal and material populations are categorized with respect to the pollution concentrations and durations associated with them and are located as zones on arrowhead charts. The thrust of the paper is that these major categories and response terms need separate documentation in air qualtiy criteria documents.

1. Introduction

There are a number of different populations exposed to air pollution, populations of people, trees, crops, animals and materials. Each such population responds to air pollution in a number of different ways. Each such response correlates best with a specific range of concentration-duration of exposure combinations. Although this is not a new concept, it has not heretofore been fully elaborated. The purpose of this paper is to show how to differentiate these several concentration-duration combinations on a concentration-averaging time -frequency of occurance (arrowhead) chart (1).

It has been noted before (2,3) that to be meaningful air quality standards stated in terms of different averaging times should be on the same percentile line on the arrowhead chart. While standards tend to be points on or near such lines, criteria documents deal in ranges of concentration-response data rather than in points, and,in addition,reflect such factors as the fatigue and acclimitization responses of human organs.

2. Short, Intermediate and Long Term Responses

Population responses tend to separate themselves into short, intermediate and long term responses, the short term ones being characterized by response times in seconds or minutes, the intermediate term ones by response times in hours or days, and the long term ones by response times in months or years. Each of the principal population categories, human, animal, vegetation and material have such tripartite response groupings (Table I).

TABLE I
Examples of Population Category Characteristic Response Times

	Characteristic Response Times		
Population Category	Short Term (Seconds-Minutes)	Intermediate Term (Hours-Days)	Long Term (Months-Years)
Human	Odor; Visibility; Nasopharyngeal and eye irritation	Acute respiratory disease	Chronic respiratory disease; Lung cancer
Vegetation (Animals)	Field crop and ornamental plant damage		Fluorosis of livestock; Decreased fruit and forest yield
Materials	Acid droplet pitting Nylon hose destruction	Rubber cracking; Silver tarnishing; Paint blackening	Corrosion; Soiling; Materials deterioration

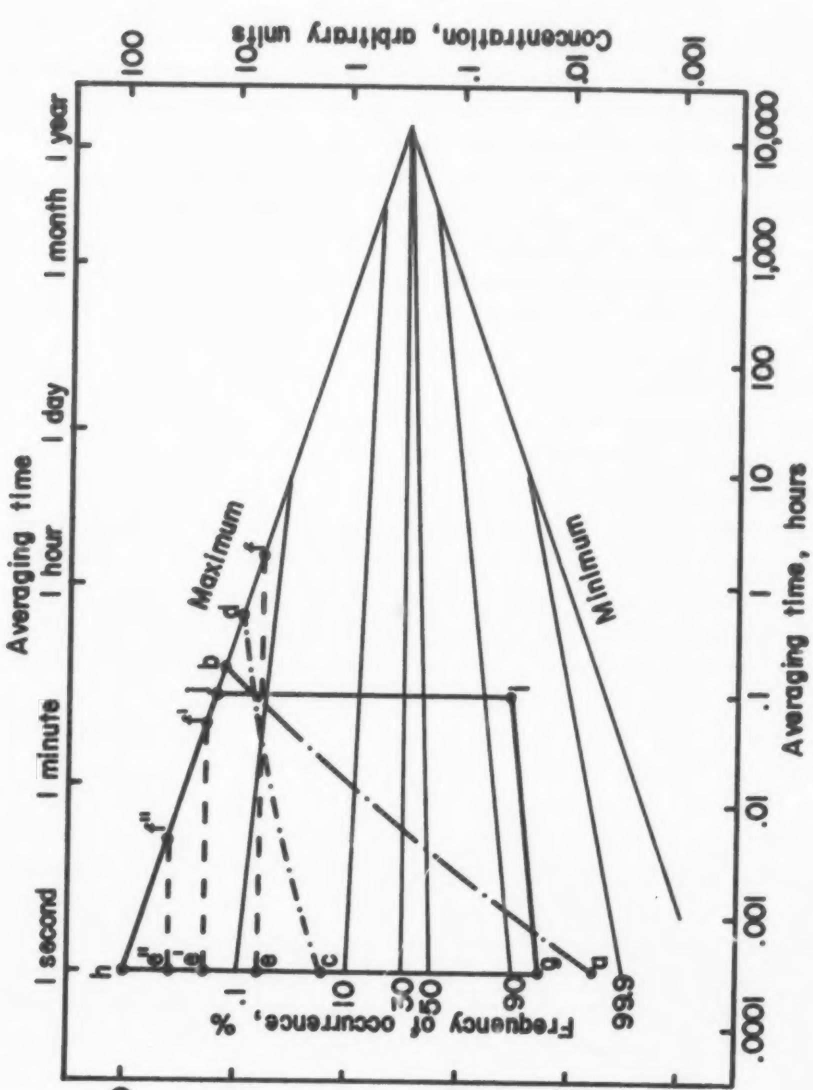


Figure 1. Short Term Responses

a - b - Odor Response, e.g. to H_2S
c - d - Eye Irritation Response, e.g. to Oxidant
e - f - Visibility Response, e.g. to Suspended Particulate Matte
  e - f - One hundred mile visibility
  e'-f' - Ten mile visibility
  e"-f" - One mile visibility
g-h-i-j - Materials Response, e.g. to Acid Droplets

3. Short Term Responses (Fig.1)

The short term responses of the several populations are quite diverse. Odor is characterized by the ability of the nose to detect extremely low concentrations but, because of odor fatigue, to rapidly lose the ability to respond to ambient concentrations. Point, a, is the odor threshold, which is known. Since a single inhalation, requiring approximately a second will establish the presence of odor, point, a, is located at 1 second. The ability to recognize the odor is lost due to odor fatigue at point, b, which is on the maximum ambient concentration line at a duration that has not been well established by experiment but can be at about 10 minutes. The shape of line a-b, which depends upon the odor fatigue time-concentration relationship is also not well established experimentally.

Nasopharyngeal and eye irritation have higher thresholds than odor and exhibit the fatigue phenomenon to a lesser, or even negligible, extent. Nasopharyngeal irritation and odor thresholds for substances with irritant properties have not been well differentiated. The instantaneous exposure threshold point, c, is arbitrarily placed at 1 second. If we assume some acclimatization of the eye to the instantaneous threshold after extended exposure, the effective threshold after a number of minutes will be point, d, which is at a concentration somewhat higher than the instantaneous threshold value, c. Neither the exact location of, d, nor the shape of line c-d are known from experimental data.

Visibility is a human response since it is what the eye can see. It correlates with suspended particulate matter concentrations in the air and has a threshold value of suspended particulate matter for each value of visibility, expressed in kilometers or miles. Thus line e-f, for a hundred mile visibility is at a lower pollutant concentration than line e'-f' for a ten mile visibility, or e"-f" for a one mile visibility. If there is a functional relationship between the concentration and size distribution of suspended particulate matter, it would affect the locus of these several lines. As shown on Figure 1, the possibility of such a functional relationship is ignored.

Typical short term responses of materials are pitting of metal and painted surfaces and destruction of nylon hosiery by acid droplets, and acid bearing solid particles, such as acid smuts. Since damage rapidly follows attack, it can be depicted as starting at one second, line g-h, and terminating in a matter of minutes of exposure, line i-j. The threshold concentrations of droplets or particles, line g-i, is arbitrary and is at a low level, below which damage from pollution cannot be differentiated from that from other sources. Line g-i, is not known from experimental data.

4. Intermediate Term Responses (Fig. 2)

The short and intermediate term response of vegetation to higher levels of certain pollutants can be measured in two ways, biologically and socio-economically. Air pollution damage to field crops and ornomental annual plants is better measured in socio-economical terms than in terms of more subtle biological response. In these terms, up to a certain level of biological response,k, there is no socio-economic loss in the sale value of the crop or the ornamental value of the plants. At a higher level of biological response, l, there is 100% loss of sales value of the crop and of ornamental value of the plants. These responses are related to dose, ie., concentration times duration. When these response (loss) curves k-k' and l-l', are transferred to an arrowhead chart, they depict the short and intermediate term responses of field crops and annual ornamental plants to ambient pollution levels. It should be recognized that the arrowhead chart must be for the location where the crop or plants grow, and that there is a paucity of such data for rural agricultural areas.

The principal intermediate term human health response is acute respiratory disease such as has occurred during air pollution episodes. The biological response involved is a dose-response curve, which for constant concentration becomes a duration-response curve. The shape of a duration of constant concentration-response curve for acute respiratory disease reflects the ability of the human body to cope with short term ambient concentration respiratory exposures and the overwhelming of the body's defenses by continued exposure. When transferred to an arrowhead chart the curve has an induction point, m, at the maximum concentration line at about a day and continues to the concentration level, n, where continued exposure can no longer induce acute disease.

A number of manifestations of material response, e.g., rubber cracking by ozone, require an exposure duration long enough for the adverse effects to be significant economically, ie., attack for just a few seconds of minutes that does not affect the utility of the material for its intended uses is not significant, concentrations

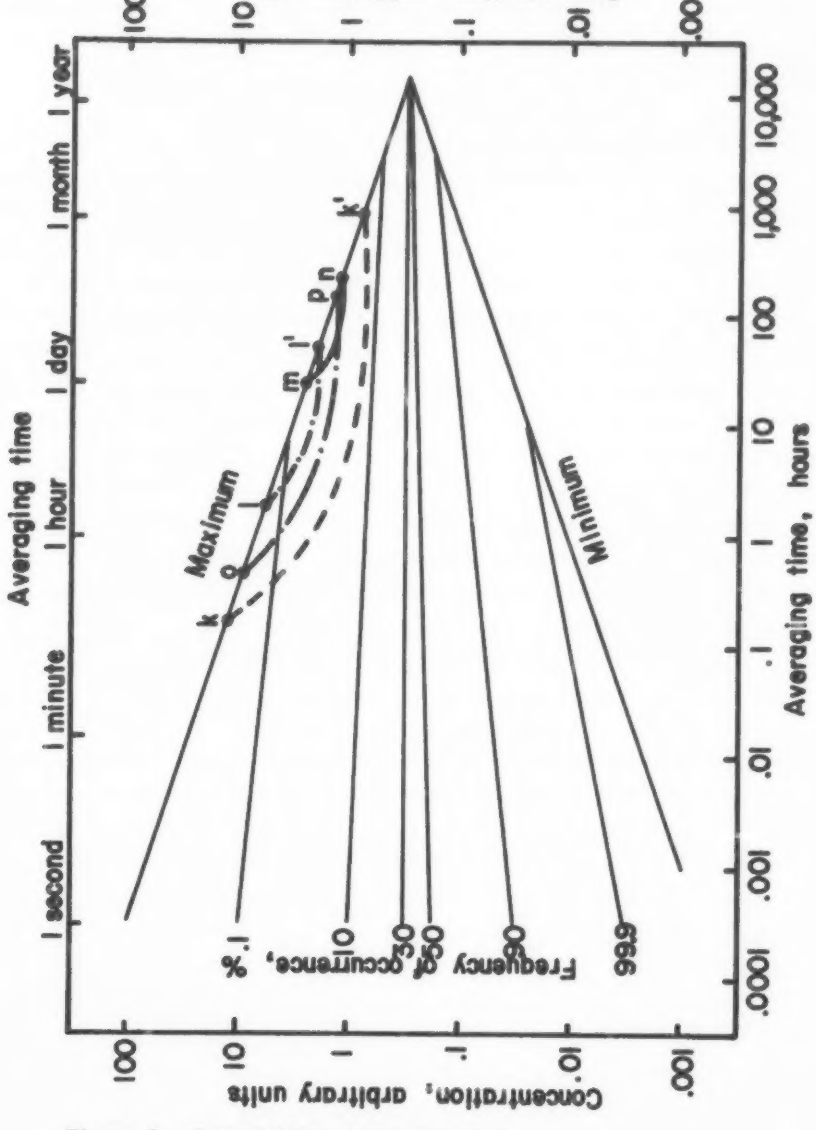


Figure 2. Intermediate Term Responses

k - k' - 0% crop loss e.g. to SO_2
l - l' - 100% crop loss e.g. to SO_2
m - n - Acute Respiratory Disease Response
o - p - Materials Damage Response
e.g. Rubber Response to O_3

less than point, o. This would be the case for rubber exposure to ambient concentrations of ozone. Conversely utility can be destroyed by a number of days of exposure (point p).

5. Long Term Responses (Fig. 3)

Fluorosis of livestock from ingestion of forage with high fluoride content has a point of induction, q, which does not occur until there has been a long enough period of deposition of a high enough ambient concentration of fluoride to build up the level of fluoride in the forage. Since the forage is either eaten by livestock or cut for hay at least once a growing season, the duration of desposition ends after the growing season (point r). The longer the duration of the season, the greater the time for deposition, hence the shape of line q-r.

The long term human responses to air pollution-chronic respiratory disease and lung cancer; the long term vegetation responses-decreased yield of fruit and forest; and the long term material responses-corrosion, soiling, and materials deterioration, all occupy the same zone, s-t, on the arrowhead chart.

It is not possible to closely differentiate intermediate and long term respiratory response so that there is overlapping of these categories.

6. Conclusion

A characteristic of all the charts presented in this paper is that the response curves stay put on the concentration-duration axes, but the arrowhead chart moves up and down depending upon whether a community's air is polluted or not polluted. This is most apparent in the case of long term responses where in a non-polluted community the long term response zone can be completely above the maximum line of the arrowhead chart, or in a highly polluted community the response zone can completely engulf the arrowhead chart down to the minimum concentration line.

There are important aspects associated with the geographic distribution of these several populations with respect to the geographic occurrence of short, intermediate and long term exposure which could not be covered in this paper due to space limitation. The general thrust of this paper is that there are three major population categories and three major response terms, short, intermediate and long, that each need separate documentation in air quality criteria documents.

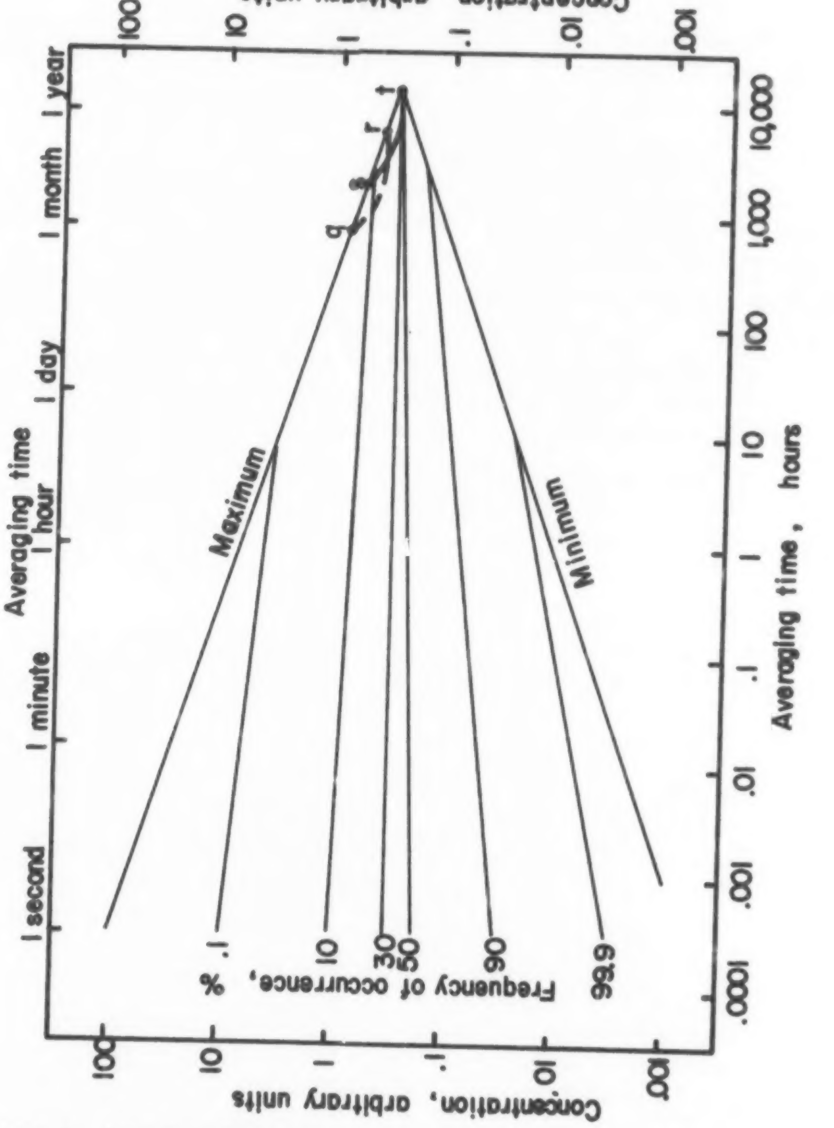


Figure 3. Long Term Responses

q – r – Vegetation/Animal Response e.g. to Fluoride
s – t – Human Response –
Chronic Respiratory Disease – Lung Cancer
Vegetation Response –
Decrease yield of fruit and forest
Materials Response –
Corrosion, Soiling and Materials Deterioration

References

1. R. I. Larsen, "A mathematical model for relating air quality measurements to air quality standards", U. S. Environmental Protection Agency, Research Triangle Park, North Carolina, Publication No. AP-89 (Nov. 1971).

2. R. I. Larsen, "Important Factors for the Sulfur Oxide Concentration in Central Stockholm", Atmospheric Environment, Vol. 6, pp. 423-426 (1972).

3. H. Shoji and T. Trukatani, "Statistical Model of Air Pollutant Concentration and its Application to the Air Quality Standards", Atmospheric Environment, Vol. 7, pp. 485-501 (1973).

215 3

PANEL DISCUSSION

Preceding page blank

SUMMARY OF DISCUSSION

SCHNEIDER (Netherlands)

Following the short statements made by the panel members, I feel that the discussion should now center on three questions:

- do we need monitoring at all;
- the way of monitoring;
- what kind of monitoring we need.

I hope we can also have a short discussion on the way we use the data that we acquire and receive from the monitoring systems.

DISCUSSION

Before we talk about monitoring needs, we actually have to ask ourselves the question do we need monitoring? I know the feelings of the panel on this so I do not have to ask them if they think it is worth while to monitor but I know there is a difference of opinion within the panel about the way the monitoring system should function or the way monitoring should be done; and I think it is worth while bringing it up later on. I would like at this stage to ask the audience whether some of the participants have a very strong feeling about the need for monitoring, if there is someone who says I do not need your monitoring at all, let him stand up and say so because we would like to solve his problem first.

Preceding page blank

LAUER (U.S.A.)

Is it better to have source monitoring with an appropriate model or monitoring of the population exposure burden?

SCHNEIDER (Netherlands)

I understand your question, and I am glad you asked it because now I can use my prerogative as a Chairman. I did ask the question, "do we need monitoring?" And you answered, "yes." You only questioned the kind of monitoring, this is the second part of the question. I really want to know if someone questions the monitoring at all. If not, I am willing to answer the second part.

MAGE (Denmark)

Like all questions I can argue equally well on both sides, so let me just say that the answer to Lauer's question is yes and no. I believe that it is better not to have any data at all about air pollution levels than to have bad data which is non-representative, or which had been taken by instruments which have not been calibrated properly, or which are taken at a location which is non-representative and you have no idea of the distribution of air pollution. You don't know whether its a high location or a low location. When one has bad data, it confuses the issue considerable. We need good data which is designed properly, and not bad data.

GOLDSMITH (U.S.A.)

Monitoring should not be done under certain circumstances:

A. If one has several year's data from an unvarying matrix of emission sources, the only source of variation will be meteorological and measurement of pollutants is much more costly than meteorological data.

B. If the purpose of monitoring is to obtain information for protection against some hazard and there is no, or poor linkage between measurement and protective services, monitoring may give a false sense of security and should not be done.

C. If the purpose is to provide data for health purposes, then the health reactions must either be predictable or monitored along with environmental exposures and if both are not being done in a balanced fashion, it is better not to make measurements.

HÖGGER (Switzerland)

Immissionskontrollen sind zweckmäßig zur Ueberwachung der Entwicklungstrends der Luftverunreinigung. Zur Erfassung der Exposition, resp. der Gefährdung der Bevölkerung sind sie jedoch nur sehr beschränkt brauchbar. Das Ausmaß der Verunreinigung wechselt sehr stark von Ort zu Ort und im Lauf der Zeit; vor allem aber ist die Bevölkerung mobil und wechselt den Standort im Lauf von 24 Stunden immer wieder. Die Exposition kann deshalb nicht mit stationären Meßstationen erfasst werden. Kohlenmonoxid- und Bleigefährdung werden sehr viel besser durch Blutuntersuchungen erfasst als durch Immissionsmessungen.

Monitoring stations are useful for assessing trends in air pollution; for the determination of exposure or hazards for the population they have very limited value. The extent of the pollution varies greatly from place to place and from hour to hour; above all, the population is mobile and moves from one locality to another many times during a period of 24 hours. The exposure cannot therefore be established by stationary measuring devices. Carbon monoxide and lead pollution are much better determined by blood examinations than by monitoring stations.

SCHNEIDER (Netherlands)

It seems that we have drifted already into the second phase, nobody actually wants to say that he does not want monitoring. All questions are comments about the way of monitoring, and what kind of monitoring we should have. When talking about the way of monitoring we can start discussing whether it is worth while doing ambient air measurements using stations as it has been done so far, or using exposure meters, or going into a more biological monitoring of man himself. First of all I would like to ask, if there is anyone from the panel who would like to say anything about the integrated monitoring, because this is a new approach.

MAGE (Denmark)

Again one has to define what one is monitoring for. For instance as Dr. Goldsmith recently mentioned, if we are monitoring for data, for an epidemiological study we have to design the experiment very carefully to simulate man's exposure. A quick example: The dose one gets of any pollutant, such as sulphur dioxide. The number of grammes per day that one inhales is an integral over 24 hours of the respiration rate (so many litres per unit time) times an efficiency factor (we do not absorb everything) integrated over time. When sleeping, the respiration rate is only four to six litres per minute; sitting at a table, not working too hard the respiration rate is only 10 litres per minute; when walking on the street the respiration rate is between 10 and 20 litres per minute. However, most of the samples are taken by sampling at a constant flow rate. Therefore one has to treat the data and look and say well, is it worse at night, or is it worse during the day. Air pollution is not a random variable, air pollution is very highly correlated. Maximum values for air pollution occur, for carbon monoxide usually during high traffic periods; in the winter in San José, we have a radiation inversion at the surface and we get very high carbon monoxide levels, 24,25 parts per million between midnight and one o'clock in the morning. But if I am only breathing 6 litres per min. why should I rate that exposure as highly as an exposure during the day when I am breathing at 20 litres per min. So one possible modification could be, a variable pumping system, pumping at 1 litre per min. during the night and 2 litres per min. during the day, and then you would get the integrated average which would correspond to an exposure. The danger of a monitoring system which does not take this into account in the beginning, is that the epidemiologist has data now, which he is going to analyse and look for significant correlation but the data have been biased because the data had not been collected the same way that the exposed person of a target population is influenced by it. When we design monitoring systems we have to take many things into account and this is an example of a thing which makes a set of data very bad. If one is interested in corrosion of statues, the weight loss would be independent of the breathing rate and the corrosion of the statue would be as if sampled at a constant rate, but if you are interested in human exposure then you have to vary the rate.

SCHUCK (U.S.A.)

I would agree that there are many factors in determining the exposure of an individual or population at risk. However I suggest that it is up to persons responsible for data interpretation to make that simple adjustment or correlation. This can be done from a continuous monitor record, without further complexing the monitoring equipment. I am wondering if the term 'integrated' does not include more than one definition. My definition of integrated is multimedia. It is a multi-media because there are many pollutants that reach us from air, water, and food. An integrated approach is to devise a system which measures some critical point in these exposure pathways, and therefore defines exposure to the receptor. Ideally it would be nice if you had a simple test for the human, that you could test his blood and find out what his exposure is to a given pollutant. With something like lead and many other materials this is not possible because once you study the entire system of the exposure pathways plus the rate of transfer of this lead, once it is absorbed into the blood, you have another entire system that is concerned with the deposition in bone, the elimination in urine, the deposition in hair, transfer into the central nervous system. Thus, this measure is very crude and has not been related to exposures.

BRAVO A (Mexico)

I wish to comment on the type of monitoring that has been in operation in Mexico and South America for at least 9 years operated by the Pan American Health Organization and the countries involved. There has been since its conception, a serious doubt as to the validity of some of the measurements of the PAHO Network such as suspended particulates in the air.

The method chosen by PAHO and used in Mexico for this particular parameter was the Warren Spring Laboratory (U.K.) method based on reflectance of the particulate matter collected on a filter, using inexpensive instrumentation.

This method was suitable for U.K. or countries which use coal as a source of heat; however, as your are well aware, in Mexico we have very little heating and the fuel we use is not coal. In a research work undertook at the University that at the same location in the same time period, the PAHO network reported an average particulate loss of 80-90 mg./cm^3; however, the estimation of this parameter with a High Volume sampler by the University indicated an average of 250 mg/m^3. Consequently, the data published by PAHO is misleading since Mexico would not be considered a city with a suspended particulate problem. Therefore, this data should be used with a great reserve if used at all for health studies, control engineering studies or in definition of air quality.

For monitoring in countries with little money and qualified human resources I believe it is better to collect fewer data but data that can be used with some sense of validity.

Source sampling applied to mathematical models in Mexico City would require a great amount of research due to our unique meteorological and topographical conditions.

BRAVO-A (Mexico)

Monitoring is needed, but the validity of the measurements should be a must.

SCHUCK (U.S.A.)

I believe that we did not answer the original question which was, how best to monitor? Why could we not use source monitoring and then a model to predict. Well there are many models that have been developed and for some point sources they are reasonable, but in general these models, even knowing quite a bit about the source and the meteorology of the area can one predict within 100% of the real value 50% of the time? That is not good enough for defining exposure pathways for example. So there is a need for all types of monitoring. Actually it depends on the mandate for why, when you ask the question why are you monitoring? Usually you will find a basis in law, and if that law requires source monitoring, then that is what you will do. On the other hand, many of the laws are stated in terms of air quality. Disregarding for a moment the unreasonableness perhaps of some of the air quality measurements depending on their location, when this is called for, you must monitor and you cannot depend on the model.

SCHNEIDER (Netherlands)

Before opening again the discussion. I would like to make just one distinction. There are clearly two points brought up here. One by Dr. Mage; when we talk about exposure monitoring do we not have to simulate in some way the intake of the pollutants, or do we go on using a constant flow. The other point which was brought up by Dr. Schuck was the integrated monitoring in the sense of the multi-media monitoring. I think these are two different questions, the first case is more or less restricted to inhalation of air pollutants, the second case is indeed a multi-media problem, when you have the same kind of pollutant in air, water, food and maybe even other media. So I would like to divide it up into two so as not to confuse the issue. To start with the first one raised, I would like to hear from the audience what they think about the question raised by Dr. Mage of a simulated flow rate.

BATES (Canada)

It seems to me that the purpose of contrasting 'personal' monitoring and 'station' monitoring is to give us an indication of the safety factor that has to be built into a standard. This leads to two questions:

1. Does the personal average level of exposure generally correspond with the station measured average, but with swings both above and below it?
2. Do you find any general 'constant' that relates the maximal pollutant exposure you may get, given a normal level of activity of the person, to the station measured average?

MAGE (Denmark)

I would like to return to figure 2 of my paper. The bars represent the actual collection of the sample. The periods between the bars were when the bags were being put away in the car, so what you see there is approximately 30 five minute random samples during that period, and from the number of samples from the arithmetic average and the standard deviation about the mean of this distribution, we could reject the null hypothesis that the air quality on the street level, 2.6 km. away from the monitoring station is the same as at the monitoring station. The other question: is there in general constant ratio between maximum exposure and average exposure? One must sample the distribution. In order to define most distributions one must know two parameters. The arithmetic mean which you could get by bubbling for example through a sulphur dioxide reagent for a year, will be a very fine measurement but you will have no information at all of the standard deviation of daily averages about that mean. So the answer to your question is, that if you tell me with what confidence level you will wish to know the maximum value that a person can be exposed to, whether you want to know it at 99%, 95% or 90%, then I will tell you how well you have to monitor. If you want a 100% confidence level, as is required in radiation exposure, every employee of the reactor must wear a radiation badge, but in air pollution I do not believe we have to have an infinite number of monitors; we can take the data and treat it statistically and make estimates as to the maximum exposures.

LAUER (U.S.A.)

Prior to modulation of the intake volume it is necessary to understand the uptake mechanism for the actual pollutant in question; the mechanism may be 1st, 2nd or 0 order with respect to the concentration.

MAGE (Denmark)

Yes, one has to know the uptake kinetics if the model is that the intake is simply a function of what you have inhaled, and this is really what you are measuring with a constant volume flow-rate like a 24 hour OECD type measurement, you are getting an average but it is a non-weighted average. If one is breathing twice as fast during the day than at night, then one will breath in twice as many carbon monoxide molecules in the same time. The 8 hour CO standard is based on an uptake ventilation rate of sedentary people. A pedestrian who is walking on the street is breathing at around 15 to 20 litres per min. and so he will reach a higher level of carboxyhaemoglobin than the sleeping person who is exposed to the same 'CO' concentration.

O'KEEFFE (U.S.A.)

I suggest that it is appropriate for the epidemiologist to attempt to refine his data according to the variable-intake concept upon a given concentration exposure; that it would be usurpation for the physical scientist to attempt to force that calculated modulation on the epidemiologist.

SCHUCK (U.S.A.)

Is it correct Dr. Mage that those 5 minute bag samples represented the condition for a person walking along a street, in other words a pedestrian on or near a street and if so the average for the entire area may be much closer to the continuous measurement than those high peaks shown by these 5 min. bag samples?

MAGE (Denmark)

The five minute samples were taken, as it stated in the paper at breathing height which was defined at approximately 1.6m. The man would walk and hold his air sample intake at nose level. He was walking just like the pedestrians stopping for traffic lights, walking across the street, passing cars which were idling and walking on the street again. This exercise was aimed at finding out really how well monitoring station measurements relate to the data from such a random approach. We have also done another study. We randomly sampled, by laying a grid over a city (San José and Copenhagen), using random numbers we generated coordinates on the grid and we went to the randomly selected locations and we sampled randomly. We do not get the same value at each place, but we get a distribution of values, and of course if one did this for a very large number of samples you will find that you can demonstrate at a fairly high level of significance that there is not a constant average value.

GOLDSMITH (U.S.A)

While I agree with the principle that a monitoring station is most valuable when it "breathes" the same way a population sample does, I do not support the proposal to weight the sampling rate by the diurnal variation of the respiratory or ventilation volume. As Prof. O'Keeffe has said epidemiologists are willing to weight the set of valid data obtained. In addition with use of twenty-second breath holding, the expired air analysis for carbon monoxide permits use of human blood in the body to be read as a monitor.

The most obvious problem of unrepresentative monitoring is in connection with emergency action based on a monitoring reading. It is of great importance to know whether the high-reading station, which is proposed to be used, represents with validity the exposure of a real population.

I do not agree with Dr. Schuck that blood lead levels are not useful for monitoring lead in air. As long as the exposure is steady over a period of months, blood lead levels may vary with atmospheric exposures (above a level of about 2 $\mu g/m^3$. This makes them useful for monitoring population levels in population groups which have only slowly changing exposures. This illustrates the point that long-term average levels for lead are all that needs to be known in order to estimate the health impact of exposures. Hourly or daily averages add little or nothing to 30 day average as a source of information related to health effects.

SCHNEIDER (Netherlands)

We should discuss now the use, or the potential use of exposure meters, the ones described in the paper by Altschuler and O'Keeffe. Is there anyone in the panel who would like to comment on the use of exposure meters versus let us say ambient air monitoring or any other kind of monitoring?

O'KEEFFE (U.S.A.)

We discuss in the paper three general types of such exposure meters that are imaginable. One would be a physico-chemical type, which would include the optical devices. We ruled the optical devices out as being mechanically not adaptable to personal dosimetry. I cannot imagine an optical absorption based instrument that could be put together with sufficient mechanical stability that it could stand the stresses of being carried around on a person; nor could it be of a size adaptable to that use. Therefore these were given quite low priority. A second class depends on the transfer of energy triggered by the presence of the pollutant to be measured. This would include such devices as the ethylene-ozone device which operates on the principle of luminescent reaction between ozone and ethylene. This obviously can very readily be miniaturized, perhaps-hopefully-to the point where it can be readily carried around on the person. Other members of that family of luminescence instruments pose much greater problems in miniaturization, but it is not beyond the bounds of imagination that they could be so miniaturized. The last category in the physico-chemical class would be that of the so called electro-chemical devices; the Ecolyzer would be an example. These measure either amperometrically or coulometrically the oxidation or reduction of the given pollutant. They lack sufficient sensitivity for dosimetric use at the present stage, because such use requires the ability of responding to background levels of the pollutants of interest. I would safely predict that this minor defect can be overcome. They have not yet been fully miniaturized, but I consider that a purely mechanical or engineering problem. I think there is great hope for this type of instrument. Now a third category is that of the sorption device. In principle it goes back to the type of air monitoring we did 5, 6, or 10 years ago. In our present thinking it tries to avoid the difficulty of working with aqueous solutions, because these would pose obvious difficulties in a personal dosimeter. Instead it proposes to use solid sorbents which would either ad-or absorb the pollutant, with a modest degree of specifity. After a given period of exposure which can be selected, they will be transported back to the laboratory and there, in the simplest case, they would simply be heated to effect desorption and the product would be carried into one of the present day ambient air monitoring instruments for an instantaneous read-out.

SCHNEIDER (Netherlands)

I think we are here at an important point, a starting point in the development of not a new technology but let us say a new generation of monitors. There has been in the past, and certainly in recent times, many comments on the use of existing and maybe even on the planned monitoring systems with respect to the correlation with health data, and I think quite correctly so in many cases. You heard from Dr. Bravo, for instance, of problems he met in Mexico. The original monitoring systems were not planned essentially for the purpose of correlating their measurements with health data and explain them. It is different I think for the type of monitors that Dr. O'Keeffe has described. These are especially intended for the combination of environmental monitoring and health data. It would be very valuable if we could hear some comments on this new approach.

MAGE (Denmark)

Dr. O'Keeffe indicated a concern about low levels. I do not think that we really have to worry about measuring such low levels. One can in terms of statistical analysis work with a censored distribution and use that part of the distribution that one can measure; at low levels there is little effect. I really do not want to know when an instrument is in the noise level near zero whether it is 0.1 or 0.2 ppm, it is sufficient for me to know that it is less than 1 ppm. This should not really be much of a bottle-neck in the development of instruments.

O'KEEFFE (U.S.A.)

In our early planning on this subject we have arbitrarily assumed that a minimum integration period of one hundreth of a day or 15 minutes would be satisfactory.

BENARIE (France)

Monitoring networks allow four-dimensional mapping of the isopleth contours (one dimension being the time). The usual ten or twenty station network gives a very weak spatial resolution. Imagine now an isopleth map with a perfect, an almost infinite resolution. This, like the 1 to 10.000 surveyor's map can be used to give a road, a land use, a political...etc., map. In the same way a perfect isopleth map can give information about human exposure (the subject moving on the four dimensional surface); an imperfect one will not.

Regarding personal monitors, we shall look for the "old" methods also: rubber cracking for ozone, sulphation plates for the SO_2, etc.

O'KEEFFE (U.S.A.)

We are quite aware of these older methods, and it is advancement on these existing methods that I have in mind when talking of the solid sorbent type of collector for return to the laboratory, for analysis. You mentioned the rubber as a collector for ozone. We actually have a very small project under way in which rubrene, which is a polycyclic hydrocarbon, reacts with ozone instead of the rubber. It is a simplified analogue of the rubber: upon return to the laboratory, when we get a objective instrumental read-out, rather than a human observation. A read-out in terms of the rubrene would be that its adduct with ozone is theroluminescent, and upon heating to 50°C it gives off light in proportion to the integrated concentration of ozone to which it has been exposed. I cite that as an example to say that we are aware of the old ways; we think that they need to be developed to the point where they give rapid simple read-out methods.

MAGE (Denmark)

Regarding the question whether it is necessary to know the location I think it is yes. If one is looking at something which is not an ambient pollutant but which is generated within the home such as cigarette smoking where there might be somebody lighting a match which will give sulphur dioxide close to your exposure meter. Something like this might happen but you would not want to tell the big refineries that they are putting out too much sulphur dioxide because somebody was lighting matches near his exposure meter and so I think one should know something of where the person has been, so that one can estimate whether the air pollution which one is measuring is ambient or whether it is residential or occupational exposure. The other question is to whether one has to know something about the movements of the people. I think you might look at it this way, if the air pollution monitoring station which is fixed in space operates in an "eulerian" framework because it is fixed in space and different gas puffs come to it in time a person is rather "lagrangian" because he is moving, he has a moving frame of reference, and so as one can talk about lagrangian correlation coeficients and eulerian correlation coeficients, it should be possible to,from the analysis of the monitoring system,get some kind of information on the movement of the person in the system. So since we certainly are not going to do this with a 100% confidence level, we have to be able to make some assumptions and accept some reductions in confidence of our results.

STEELE (U.S.A.)

One cannot argue the premise that "good" data may be beneficial for a designated information use, and that "bad" data may be detrimental or misleading. The difficulty comes in setting criteria (specifying purpose or use, pertinent variables (pollutants), statistical measures of concern relative to each variable, frequency and schedule of sampling to achieve those measures, and the latter leading to desired or required accuracy of measurement) on what constitutes "good" or "bad" data. Specification of criteria depends greatly upon use of the obtained information (that is in this case impact on policy, on decisions involving environmental health effects or standards). Also economics plays a critical note. At some point in evaluating data-monitoring programs, one reaches a point where the incremental allocation of resources to improve the accuracy of some measure or to provide additional information may not be "worth" it (worth commonly being a value judgment based upon some designated consensus).

In the field of water resources, for which I am more familiar, several studies here have been carried out to help in determining the "worth" of certain hydrologic data, including those for water quality variables. Are there examples of parallel studies (completed or ongoing) in the field of assessment or monitoring of air pollutants?

SCHUCK (U.S.A.)

I will attempt to answer the question concerning the modeling. There is a great deal of effort within EPA, within the modeling field both in terms of specific models for point sources for example and more general atmospheric models that would apply to an urban area. There is a very major EPA effort called the RAPS in St. Louis, in which a data basis is being generated with an array of stations for the very specific purpose of testing out these very complex urban models that have been developed. St. Louis was chosen because it was the simplest case in the United States and somewhat representative of many other cities, it is not near a large body of water, it has relatively a flat terrain, it does not have other major sources close by. The object was to find the simplest case first because, simple as it is it is extremely complex.

O'KEEFFE (U.S.A.)

I would like to comment from a somewhat different point of view on the same question. Basically we have two different types of monitoring, one of these is that done to determine whether or not we have attained a legally required level of air quality. This is a legally motivated operation and the tendency is to demand the extreme of precision in such measurements because after all it has a legal background and eventually it will get to court and the attorneys will argue over the last significant figure until they tire themselves out. On the other hand we have, and my feeling was that today's discussion was confined to this, the use of monitoring as a tool in epidemiology. There I believe that we can tolerate rather a larger uncertainty, plus or minus 25% perhaps would be quite tolerable.

SCHNEIDER (Netherlands)

We are supposed to be talking only about monitoring needs in relation to health. I know it is difficult, I already warned both the panel and the audience about the trap that one can fall into when talking about monitoring needs. Monitoring is a whole field and we are only supposed to be talking about part of it. Although I know that there are some economists within this audience, I think first comes the question that is being asked by the epidemiologists or others from the medical field. One finds any kind of monitor or monitoring system one needs to answer the question and if this interferes with finance or economy one starts to design it again. But I think the answering the question should come first. Although I know it is a very interesting subject, the subject of the exposure meter, looking at the clock, I would like to close this one and go to the next. Moving to integrated monitoring, in the sense of the multimedia approach mentioned by Dr. Schuck. I know of a few other institutes and agencies besides EPA who are working in this field. Here also we need to put in a large effort to get some small results out of it, and here also it is important to know, or to get a feeling whether it is worthwhile.

SCHUCK (U.S.A.)

This subject of integrated monitoring design is a fairly all encompassing one, it does take into account cost benefit for example, it does take into account the number of stations. I think if you reflect on our environment and our present concerns they seem to be increasing each year. If we do not take a careful look at, and plan our monitoring we will be spending unreasonable resources on such activities and that really is probably the basic point behind this charge we have in Las Vegas to examine in detail monitoring systems and this includes existing monitoring systems. Are they adequate? Are they (they were planned many years ago) still fulfilling their mandate? Are there too many stations involved for example? There are indications from some preliminary work that perhaps in large geographical areas, because of the over-riding influence of gross meteorological factors perhaps one station instead of 25 in several thousand square miles might be sufficient, depending on how accurately you wish to define the level (in cases where there is a very definite proportionality, between the reading at one station and another station 50 miles away). This may not apply to all geographical areas. The geographical area that I am speaking about is in southern California where stable conditions prevail, but within reason I believe that we will find many areas where we can reduce the number of sampling stations. Certainly we have to take a hard look at how much monitoring we do. Again there are some requirements (legal) but do we have to go beyond that? If we have in fact enough research information to have defined the exposure pathways, need we sample continuously? If indeed there is a need for research perhaps that has long since been satisfied, and now one is merely fulfilling the requirements of the law, in that one is watching the levels to see whether one's control measures are having their effect. One may then be able to get by with much less expenditure in funds for monitoring activities, when viewed from that angle.

We have this concern because of the very large cost of monitoring the environment.

MAGE (Denmark)

Talking about costs, there are two different magnitudes involved. If one talks about costs to the American automobile industry of the model changes and to the industries throughout the European area who have to modify their vehicles to be sold in the American market, it is a very large cost. Much of these modifications are made in relation to air pollution air quality data in terms of what reduction of emissions is necessary to meet an air quality standard. If one had better information perhaps one might be able to reduce the emission reduction. For example, if one spends, lets say one hundred thousand dollars, and got more precise measurements then one might not have to spend a billion dollars but only 900 million saving one hundred million for an expenditure of only one hundred thousand. I think perhaps more monitoring might indeed be good if its designed properly and one knows what one is going to do with the data once one gets it.

SCHNEIDER (Netherlands)

While cost-benefit analysis is very interesting and important, our concern at present is the multi-media approach.

DUNCAN (U.K.)

Epidemiology requires accuracy of monitoring to a high degree and this then has to be for a limited programme. If you talk of routine monitoring the accuracy may not be so important, it depends on the realism of the standards to be met. We must be careful not to search for knowledge with routine observations. We must keep our purpose clearly defined in planning monitoring programmes.

MERIAN (Switzerland)

Does the panel agree that we should primarily monitor the most relevant pollutants? I believe that in traffic oriented monitoring hydrocarbons are more relevant than carbon monoxide and nitrogen oxides. It is however interesting to note that in this session hydrocarbons are not mentioned. Perhaps the reason is that it is more difficult to measure hydrocarbons than for instance the less relevant carbon monoxide. Should we not develop a simple instrument to monitor hydrocarbons? It is a question of responsibility to do research in fields which are recognized to be relevant.

SCHNEIDER (Netherlands)

Regarding the question on accuracy I feel that 25% accuracy might be enough for epidemiology and maybe we could do with the same accuracy for other purposes. What is necessary is that we answer the question asked, and so far the questions being asked by our medical colleagues is to give and answer plus or minus 25% as a rough guess. If you talk about other questions you may need a much higher accuracy to answer the question.

Regarding hydrocarbons, I think Dr. Merian perfectly right, at least for certain regions. I can answer you by naming a few regions in my own country and I know many more in western Europe and all over the world. The point is that here again, we do not have at the moment the possibility of measuring hydrocarbons with exposure metres. But if there is a question, and if there is a problem, I think that such a monitor should be developed.

SCHUCK (U.S.A.)

Generally speaking the choice of the pollutants measured in routine monitoring at least in the United States, has to do with the selection of pollutants which have been studied in detail, and for which national air quality standards have been established. Beyond that much of it is still in a research stage. I would think that what should be the highest priority on the list might depend to some extent on what region, what country we are talking about.

MAGE (Denmark)

To respond to the question as to why do we not measure hydrocarbons, I would first like to point out that in the technique which was involved in the paper which I presented were samples collected using aluminized mylar bags. Assuming that it is nothing like ozone or nitrogen dioxide which would chemically react in the dark atmosphere, the same technique could be used for anything, since you can go back to your laboratory with the bag and put it on the gas chromatograph. When you are talking about hydrocarbons one has to be careful because these are personal type exposures. If one is interested in a breakdown into carcinogens or chemically reactive species in the photo-chemical oxidant network you are asking for somebody to walk around with at least a gas chromatograph, and to my knowledge those instruments are not quite portable and vibration free, but I would suggest that one could do the type of analysis which we had authored as a means of sampling. Once the sample is back in the laboratory, if you are only interested in total hydrocarbon you can use a flame ionization unit, if you are interested in a breakdown you can use a gas chromatograph.

SCHUCK (U.S.A)

I would like to comment that I so not believe that any instrumental technique is easy. I would agree that yes we have developed instruments for certain pollutants and those are the ones we intend to monitor. I would further agree that we have research techniques for just about any other pollutant you wish to name or group of pollutants, and people are working to make practical instruments out of these. At the moment they are either much too expensive techniques, they are unreliable or require the complete attention of a well trained technician at all times, if not a professional. Many methods have been applied but not in a routine monitoring sense. The area of aerosols for example is one field where much work is being done and probably more research is required in that field than any place else. Work is going on on acid aerosols but at the moment our best technique is a rather gross measure, it is a total measure of the amount by weight of particulates in the air, and that is about the least amount of information, the least useful amount of information that we can get. Yes there are complex techniques that can go beyond that, but they cannot be applied routinely yet.

OREL (U.S.A.)

Much has been said at this conference about the problems of sulphates therefore I address my question, are we monitoring the right pollutants to assure public safety? when high sulphur fuel oil was burned early this year, we needed much more data on particulates in sufficient locations and sufficient frequency with this in mind?

MAGE (Denmark)

When you are asking "do we have enough monitoring," one has to know something about the standard deviation of particulate measurements. If there is a very low standard deviation (within a city) of lets say 5 or 6 stations, one does not need as many monitoring stations as when you have, in a particular area, a very high standard deviation which is a measure of the spread of the total population about the arithmetic mean of the population. So to answer your question I would have to look at the information from existing networks, look at the standard deviation of sulphate measurements, if they are all, lets say $30\mu g/m^3$ every day then I think we have enough; but if some are one some 100 , some 20 and some 4o then we perhaps do not have enough stations.

SCHNEIDER (Netherlands)

To further answer your question about more measurements, looking all over the world, I think that in general the answer is no, there are enough measurements. Especially if we talk about the total amount of particulates, but if we talk about what kind of particulates, (with sulphates among them) then the answer is not straightforward; it depends on the location. In general we could say there are enough measurements on amount of particulates, not enough on composition, size distribution and reactive properties of particulates.

SCHWING (U.S.A.)

What is the appropriate rollback model to protect the public health and what are the monitoring needs to satisfy the model. Should one monitor for peaks or averages or statistical deviations from some norm?

SCHUCK (U.S.A.)

Perhaps I can answer part of it. It does depend in a sense on what pollutant you are talking about. This is usually specified in the law that covers the pollutant.

GOLDSMITH (U.S.A.)

That depends on the health problem which has been defined, often monitoring is done for what is easy to measure and not for what is most important to health. Examples include:

1) aldehydes, which appear to be important in producing effects of photochemical pollution.

2) Monitoring of acid aerosols.

3) The present monitoring of suspended particulate matter without size distinctions or chemical characterization is so inappropriate to health considerations that the California Health Department has been advised not to consider further the standards for particulate matter until particle size data to reflect the sizes with high respiratory retention are available.

4) One needs portable or personal samplers to estimate pollution within residential premises (so called domestic pollution). Dr. Bouhuys mentioned an example of this.

MAGE (Denmark)

I just cannot resist quoting something that I have heard lately which is that "if something is not worth doing, it is not worth doing well," and I think that Dr. Schwing's question is a typical example of this type of problem that one gets into when one talks about -- lets say a linear rollback. I do not know how many in the audience are familiar with what linear rollback is; It is a simple assumption that if you reduce the sources by a factor of 2 from what they are this year the highest level you will have next year will be half of the highest level you have this year. This is an incorrect model from the simple dimensional analysis approach, because the dimensions for any kind of equation must be homogeneous and consistent. One cannot say that concentration which is dimensionless -- lets say ppm is equal to a constant which has dimensions times an emission factor which is something like mass tons per unit time per unit area. There are more than just one variable in the equation, and there is no purpose in devising a monitoring system and analysing data to verify the linear rollback model when the linear rollback model is theoretically incorrect.

SCHUCK (U.S.A.)

I would agree that the concept of linear rollback has its problems, but at the moment this is the only tool we have to approach this subject. What becomes the biggest area of concern is when you try to apply this to a secondary type pollutant such as ozone in the atmosphere. Ozone in the atmosphere is caused by the photo-chemical interaction of oxides of nitrogen and hydrocarbons, and unless you have a control programme which controls each of these variables to the same degree, then you cannot expect linear rollback to predict with any degree of accuracy what the effect will be. It is most important that this be recognized when attempting to reduce oxidants in the atmosphere, This gets back to the entire question of taking a systems approach, you cannot say that hydrocarbons are the most important and ignore what is happening to your oxides of nitrogen as has been done in some past effort to control the hydrocarbons in exhaust gases. They reduced hydrocarbons by increasing the flame temperature in the combustion chamber and thus increasing the oxides of nitrogen. It had a benefit in that the oxides of nitrogen, in this case nitric oxide reacts rapidly with ozone to destroy it, so you have an additional benefit besides reducing the hydrocarbon. At the same time, this was somewhat offset by the increase levels in nitrogen dioxide levels in the atmosphere which is also health related. Any application of linear rollback has to take into account a lot of factors, particularly if we are talking about secondary pollutants.

MAGE (Denmark)

would like to point out that it is very dangerous to use a linear model, even if it is dimensionally correct for a non-linear system. Air pollution and photochemical smog is a highly non-linear system. For instance there are regimes which have been found in smog chamber studies, where if you decrease the amount of nitrogen oxides and you increase the amount of hydrocarbons in your smog chamber you can increase the amount of ozone that is produced. You have a non-linear differential equation and try to linearize it. The assumptions that you make are vital in the confidence of the answer you get from the results of your study, and so one has to know the system.

SCHUCK (U.S.A.)

To say that we are using a linear model in our attempts to control ozone in the atmosphere is not correct. We did not use data from chamber systems, for the simple fact that they cannot be extrapolated. There is too much effect of the chambers themselves on the reacting mixtures. The model that is used for predicting the degree of control required is based on actual observations of values in the atmosphere and their variation, and it is indeed a non-linear model.

SCHWING (U.S.A.)

Though the mechanisms of photochemical smog are non-linear, models currently used are linear in that they incorrectly assume that reducing emissions by 9/1o will reduce peak values by 9/1o.

It has been demonstrated that the degree of nonlinearity is so great that the abatement requirements differ from the requirements of linear models.

SCHUCK (U.S.A.)

There are several non-linear models, including the one that EPA is currently using, and they all come up with approximate the same predicted degree of control based on non-linear concepts including the model that you have mentioned.

SCHNEIDER (Netherlands)

We have not touched upon one subject which is the form of the data and the use of the data. I know this is a difficult subject. You heard on the one side the approach used by Dr. Bravo, an index as a measure of pollution, on the other side you have the automatic and continuous monitoring giving measurement results every minute or even less, but in view of the lack of time and importance of the subject we should leave it for a latter discussion.

It is always dfficult to summarize a discussion. We have been talking about the need for monitoring, especially in connection with health. I think that it is certainly worthwhile to have second thoughts about the design of the monitoring systems. I think this was definitely a point that was made this afternoon There is a general opinion that the use of personal exposure meters should be promoted. Also clearly expressed was the wish from the medical side to monitor not only the "easy" pollutants.

GEWEBSMESSUNGEN
TISSUE MEASUREMENTS
MESURES RELATIVES AUX TISSUS BIOLOGIQUES
MISURE NEI TESSUTI BIOLOGICI
METINGEN VAN BIOLOGISCH WEEFSEL

Panel

Vorsitzender - Chairman - Président - Presidente - Voorzitter

D. SZADKOWSKI
(Bundesrepublik Deutschland)

INTERCOMPARISON PROGRAMME ON THE ANALYSIS OF LEAD, CADMIUM AND MERCURY IN BIOLOGICAL FLUIDS

A. BERLIN[+], R. LAUWERYS[++], J.P. BUCHET[++]
H. ROELS[++], P. DEL CASTILHO[++] AND J. SMEETS[+]

+ Health Protection Directorate, Commission of the European Communities, Luxembourg

++ Unité de Toxicologie Industrielle et Médicale, Université Catholique de Louvain, Brussels, Belgium

ABSTRACT

An intercomparison programme was undertaken to evaluate the accuracy and precision of lead, cadmium and mercury determinations in blood and urine. Sixty-six laboratories participated in this study. For all the analyses a minority of laboratories only measure the metals with a satisfactory precision (intralaboratory coefficient of variation of 3 or 4 measurements ≤10%). However, the laboratories which demonstrated a sufficient precision in their measurements did not necessarily determine the metal concentration with a satisfactory accuracy. It seems that at least for blood lead determinations the variability found between laboratories which measure the metals with precision is due to systematic errors.

Preceding page blank

Precise and accurate determination of heavy metals in body fluids is of paramount importance for the correct evaluation of environmental exposure to these metals.

Intercomparison programmes have been run and in some countries are routinely undertaken for controlling the accuracy of the methods used by different laboratories for the determination of lead, cadmium and mercury in blood and/or urine. In some programmes the precision of the methods has also been evaluated. In general, these studies have indicated that the reliability of these measurements is unsatisfactory (1, 2).

The study performed in 1970 by Kepler et al in the U.S. in which 66 laboratories participated showed that about half the laboratories only reported results of acceptable accuracy. This study gave also an indication of the precision of blood lead measurements since the participating laboratories recieved two identical samples wearing different code numbers. About 43% of the laboratories reported similar results (± 10μg%) for two identical blood samples containing approximately 65μg/100 ml lead. However, the range of the reported values was considerable: from 0 to 5600μg/100 ml for all the laboratories and after elimination of two "outlyers" still from 30 to 120μg%.

In 1972, the CEC ran a limited intercomparison programme (26 participating laboratories) of blood lead determination (1), which also demonstrated a great scatter of the results reported by the laboratories. However, the precision of the measurements performed by each laboratory could not be evaluated since only one sample of each blood specimen was sent to the laboratories. A more extensive intercomparison programme was therefore undertaken in which accuracy and precision of lead, cadmium and mercury determinations performed by 66 European laboratories could be evaluated by sending to each laboratory 3 or 4 identical samples wearing different code numbers.

MATERIAL AND METHODS

a. Experimental Protocol

Only unspiked samples were used. Using ^{203}Pb as tracer, Kopito and coworkers (3) have recently shown that because of differences in-vivo and in-vitro lead binding, recovery of added inorganic lead may not accurately reflect the fate of endogenous lead in some analytical procedures. The following samples were sent to the laboratories:

Blood:	Blood C: 4 identical samples (cow blood)
	Blood D: 3 identical samples (cow blood)
	Blood E: 1 sample (human blood)
Urine:	Urine A: 4 identical samples
	Urine B: 3 identical samples
Aqueous Solution:	Solution 1: 3 identical samples
	Solution 2: 1 sample obtained by 10% dilution of solution 1.

b. Preparation of blood, urine and aqueous solutions

A. Blood

1. Cow Blood

The two different bloods C and D were obtained on different times by withdrawing blood from a cow that was receiving metal salt solutions orally. The blood was taken by means of a needle introduced into a vein of the neck and connected to a 1 litre baxter in which the blood was collected under reduced pressure. The first 10 ml were discarded to avoid contamination. The baxters were treated beforehand with 10% nitric acid. After rinsing with demineralized water, sodium heparin (Roche) was added. The baxters were evacuated at the water pump. To prevent bacterial growth, blood was stored at 4°C., furthermore, 50 mg streptomycine and 10 mg chloramphenicol per litre of blood were added.

2. Human blood

The human blood E was obtained from four donors of blood group A who were not occupationally exposed to heavy metals. A total quantity of 1.5 litres was collected on sodium heparin in two 1 litre baxters under reduced pressure.

B. Urine

Urine was obtained from normal persons and from workers occupationally exposed to Pb or Hg. The samples were collected on concentrated nitric acid to yield a final HNO_3 concentration of approximately 3% (w/v). During storage in the cold room ($4^{\circ}C$) a precipitate was formed. The urine was filtrated and mixed to yield two different urine pools, i.e. A and B.

C. Aqueous solution

$Pb(NO_3)_2$ and $CdCl_2 . 2\ 1/2\ H_2O$ (pro analysis, U.C.B., Belgium) were dissolved in 1% HNO_3 (w/v) to yield a solution containing 186μg Pb and 34.7μg Cd per litre (solution 1).

The 10% lower concentration solution was obtained by dilution of the preceding solution with 1% HNO_3 (solution 2).

c. Sampling

For blood and aqueous solutions 10 ml polystyrene tubes were used (Distrilabo, Belgium).

For urine 50, 200 and 250 ml polyethylene bottles were used with internal polyethylene cap and external rad plastic screw cap (Belgolabo, Belgium). All containers were treated beforehand with 10% HNO_3 and demineralized water. Urine and blood were continually agitated during distribution. The homogeneity of the blood samples was checked by measuring the haematocrit value of several samples taken at regular intervals during the distribution.

RESULTS AND DISCUSSION

All the results are summarized in Table I. Three different coefficients of variation (C.V.) could be calculated: 1) an interlaboratory C.V. which is calculated from the distribution from the means of the independent measurements which were made by each laboratory on blood C and D, on urine A and B and on aqueous solution 1, and from the distribution of the single measurements performed on blood E and aqueous solution 2. 2) a "true" intralaboratory C.V. which is calculated from the 3 and 4 independent measurements made by eaçh laboratory (blood C, D; urine A, B and

TABLE I : Summary Table - Lead - Mercury - Cadmium

Analysis	N	Mean	Median	Range	Interlaboratory CV**(%)	"True" intralaboratory CV (%)		"Reported" intralaboratory CV (%)		
						Median	Range	N	Median	Range
Pb Blood C (4)*	52	15.0	12.8	2.7 - 49.0	52.2	12.2	1.5 - 129.2	37	7.8	0.4 - 17.0
Blood D (3)	52	24.1	22.7	10.3 - 87.3	42.9	6.8	0.8 - 99.9	38	4.4	0 - 22.6
Blood E (1)	55	23.3	18.1	1 -115	77.5			38	4.9	0 - 20.0
Urine A (4)	33	62.6	62.3	5.3 -159	58.8	12.8	1.7 - 38.1	19	4.8	0 - 19.6
Urine B (3)	34	84.1	78.3	8.4 -185.2	49.7	11.1	0 - 64.0	21	4.0	0 - 21
Aq.sol.1(3)	51	209.0	196.6	24.7 -669.8	54.9	8.3	0 - 89.5	26	4.2	0.6 - 30.3
Aq.sol.2(1)	50	193.8	190.0	18 -580	47.9			24	2.2	0 - 32.8
Hg Blood C (4)	18	4.4	3.6	1.9 - 9.4	49.7	11.5	1.1 - 46.8	10	6.6	2.4 - 28.2
Blood D (3)	18	2.8	2.1	0.8 - 11.3	86.6	15.8	0 - 86.8	10	8.4	0 - 37
Blood E (1)	18	2.6	2.4	0.2 - 9.0	80.5			10	1.1	0 -104
Urine A (4)	29	7.5	4.6	1 - 87.5	206	12.0	0 - 168	14	12.3	2.6 - 40
Urine B (3)	29	13.0	11.0	4.9 - 63.3	81.8	6.8	0 - 36.5	13	6.3	1.6 - 26.6
Cd Blood C (4)	14	1.4	0.65	0.1 - 9.2	(168)***	29.9	8.8 - 61.9	8	4.6	0 - 22.9
Blood D (3)	17	1.5	0.9	0.03- 7.3	(116)	12.8	3.6 - 28.4	11	7.4	0 - 28.0
Blood E (1)	17	1.9	0.96	0 - 11.0	(143)			11	7.2	0 - 26.1
Aq.sol1 (3)	22	38.2	35.0	18 -116.7	(51.2)	3.2	1.3 - 39.0	9	4.3	1 - 10
Aq.sol2 (1)	22	36.4	33.0	11 -150	(72.0)			9	2.0	0 - 13.9

* Number of identical samples sent to each laboratory.

** CV = coefficient of variation

*** Distribution of means deviates markedly from normality. (values within brackets)
The concentrations are expressed in µg/100 ml (blood) or in µg/l (urine).

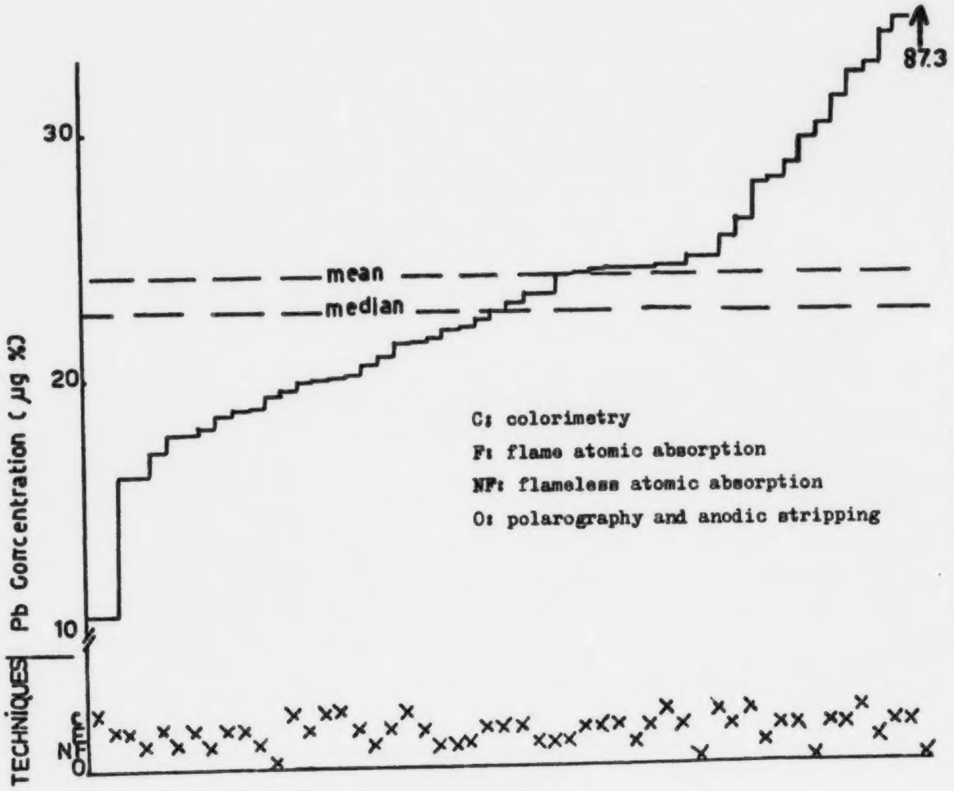


Figure 1 : Distribution of results of lead analysis on blood sample D (all laboratories). The techniques used by the laboratories are indicated by the abbreviations

aqueous solution 1). 3) a "reported" intralaboratory C.V. could also be calculated when laboratories performed several analyses on the same sample. For all the analyses the range of the reported results is very large. As expected the interlaboratory C.V. is always greater than the "true" intralaboratory C.V. It is interesting to notice that in general the "reported" intralaboratory C.V. is smaller than the "true" intralaboratory C.V. This finding demonstrates the existence of a laboratory bias in reporting results; when several measurements are performed on the same sample, obviously outlying results are rejected.

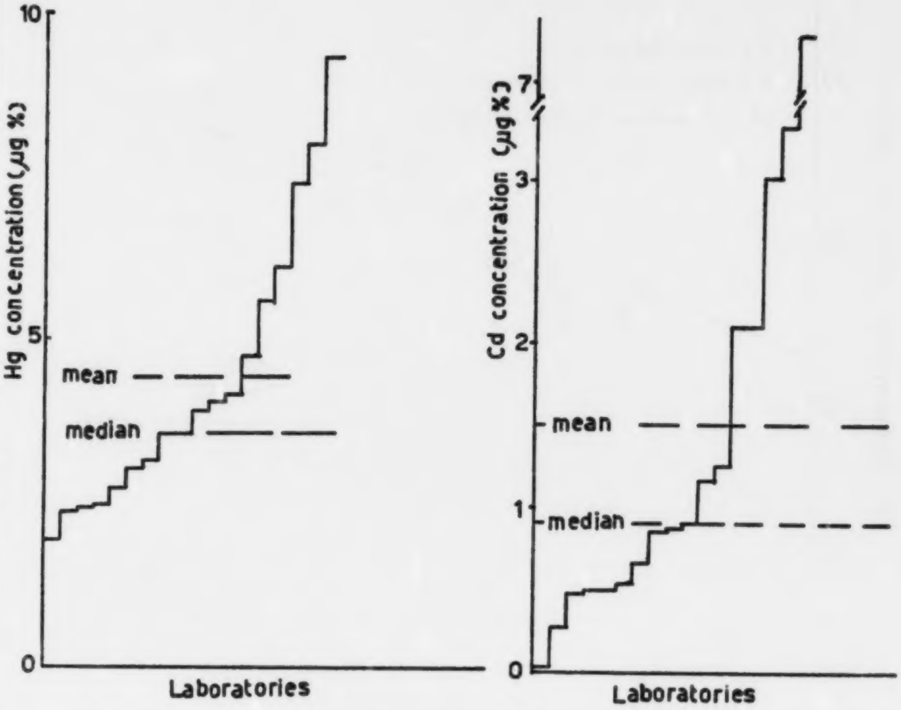


Figure 2: Distribution of results of mercury analysis on blood C and cadmium analysis on blood D (all laboratories)

Figures 1 and 2 illustrate the distribution of the mean values of lead, cadmium and mercury in the blood samples in which their concentrations were the highest (D for Pb and Cd, and C for Hg).

For lead determinations (Fig. 1) the analytical methods are also indicated. It is evident that the scatter of the results is rather similar whichever method used in this programme. We have found that the interlaboratory coefficients of variation for laboratories with high (≥30 analyses/month) or low degree of experience are not significantly different.

The interlaboratory coefficient of variation for laboratories which obtained a low "true" intralaboratory coefficient of variation (≤10%) was lower than that of the other laboratories. The

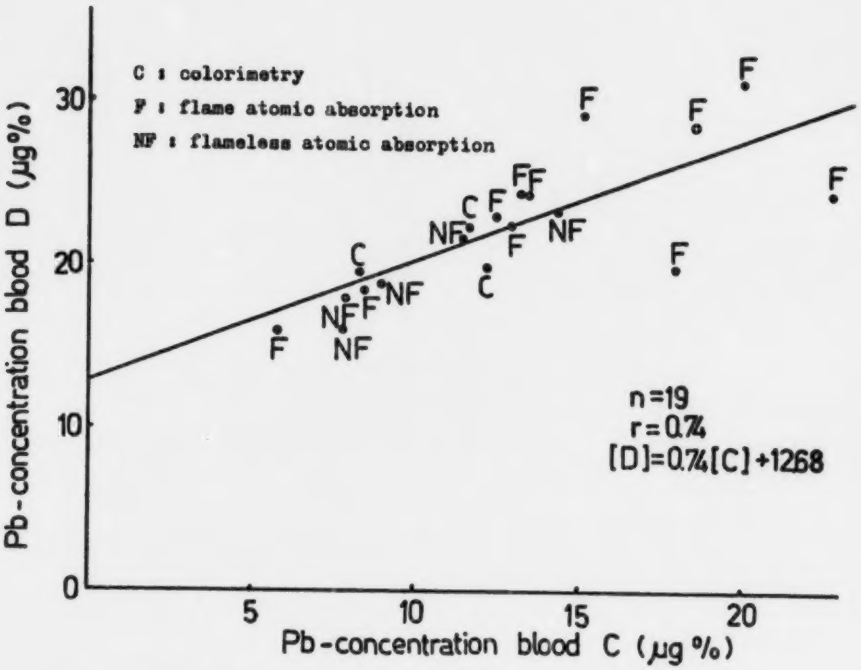


Figure 3 : Correlation between lead concentrations in blood D and C measured by laboratories with small "true" coefficient of variation. (≤ 10%) for both measurements

influence of both factors on interlaboratory coefficients of variation is shown in Table II. Although combination of both factors improves the interlaboratory coefficient of variation, the accuracy of the results remains unsatisfactory. These results suggest that systematic errors are responsible for the high interlaboratory variation observed between laboratories that measure the metals with a satisfactory precision. To test this hypothesis we have compared the results of the low blood lead (C) and the high blood lead (D) analysis obtained by the 19 laboratories which exhibited a "true" intralaboratory coefficient of variation ≤10% for both samples (Figure 3).

Although values reported for blood C vary between 5.8 and 22.3µg% and for blood D between 16.0 and 31.3µg% their ratio is rather constant; a significant correlation between the pairs of measurements is found (r = 0.74). These results support the

TABLE II : Effect of combination of small "true" intralaboratory variation (CV) and high experience on interlaboratory mean and variation.

Analysis	Laboratories with "true" CV $\leqslant$ 10 % and exper. $>$ 30 anal/month.			Other Laboratories		
	n	$\overline{X}$ *	CV (%)	n	$\overline{X}$ *	CV (%)
^{Pb}Blood C	20	13.4	34 +	30	16.5	55
Blood D	24	22.6	20 +	27	25.4	54
Urine A	5	52.6	32 +	26	61.7	60
Urine B	8	78.7	14 +	26	85.9	54
^{Hg}Blood C	5	2.81	17 +	13	4.98	46
Blood D	3	1.20	16 +	12	3.33	84
Urine A	7**	4.36	33	21	4.89	46
Urine B	11**	11.00	21 +	17	11.30	50

* The concentrations are expressed in µg/100 ml (blood) or µg/l (urine)

** 1 outlying value excluded

+ Distributions significantly different ($p < 0.05$)

Data for Cd are omitted because to few laboratories have a low "true" C.V. and a high experience.

hypothesis that the variability found between laboratories that measure the metals with precision, is due to systematic errors.

CONCLUSION

The majority of the laboratories which took part in the studies have not adequately developed the techniques required for the precise measurement of Pb, Cd and Hg in blood, urine and water.

The variability of the results is not due to the use of different analytical methods or difference in experience since precise results were obtained by laboratories using different techniques and having a different degree of experience.

Furthermore the laboratories that measure the metals with precision do not exhibit the same degree of accuracy. Heavy metal levels in blood and urine cannot therefore be directly compared when the measurements are performed by different laboratories even if the precision of their analysis is satisfactory. Therefore interlaboratory comparison of dose-response curves for different parameters (e.g. urinary δ-aminolevulinic acid, erythrocyte δ-aminolevulinic acid dehydratase...) based on the metal content of biological materials are questionable. Laboratories should exchange samples regularly and standardize further their methods for reducing their systematic differences.

ACKNOWLEDGEMENTS

While in the impossibility of listing individually the nearly seventy laboratories who have participated in this programme, the authors wish to thank them and acknowledge the fact that without their enthusiastic collaboration this programme would not have been possible. Mme Langevin deserves a special note of recognition for the coordination of this programme.

Thanks are also due to Dr. Recht for his advice and encouragement during this whole study.

REFERENCES

1. Berlin, A., Del Castilho, P. and Smeets, J., European Intercomparison Programmes, page 1033 in Proceedings International Symposium Environmental Health Aspects of Lead, Amsterdam 1972 published by the Commission of the European Communities, Luxembourg 1973.

2. Keppler, J. F., Maxfield, M. E., Moss, W. D., Tietjen, G. and Lich, A. L., Interlaboratory Evaluation of the Reliability of blood lead analyses. Amer. Ind. Hyg. Assoc. J. 31, 412, 1970.

3. Kopito, E. L., Davis, M. A. and Shwachman, H., "Sources of Error in Determining Lead in Blood by Atomic Absorption Spectrophotometry". Clin. Chem. 20/2, 205-211 (1974).

A COMPARISON OF METHODS FOR ANALYSIS OF CADMIUM IN FOOD AND BIOLOGICAL MATERIAL. A CO-OPERATIVE STUDY BETWEEN SWEDEN, JAPAN AND U.S.A.

TORD KJELLSTRÖM[+], KENZABURO TSUCHIYA[++]
EDYTHALENA TOMPKINS[+++], EIGO TAKABATAKE[++++]
BIRGER LIND[+] AND LARS LINNMAN[+]

+ Department of Environmental Hygiene, Karolinska Institute and National Swedish Environment Protection Board, Stockholm Sweden

++ Department of Public Health and Preventive Medicine, Keio University, Tokyo, Japan

+++ Human Studies Laboratory, National Environmental Research Center, Research Triangle Park, NC, USA

++++ Institute of Public Health, Tokyo, Japan

ABSTRACT

The data presented are part of the "Japanese-Swedish-United States Co-operative Studies on the Health Effect of Environmental Cadmium". In addition certain data are included from Swedish (Isotope Technics Inc., Stockholm), American (Dr. Philip D. Lafleur, National Bureau of Standards, Washington DC) and Japanese laboratories (Professor Jun Kobayashi, Institute for Agricultural and Biological Sciences, Okayama University, Kurashiki, Japan; Dr. Kentaro Kubota and Dr. Kazuko Shiroishi, Toyama Institute of Hygiene and Medical Microbiology, Toyama, Japan), which originally were not participating in the co-operative studies.

The study is a part of a larger project, including studies on the accumulation of cadmium on organs with age, on the average cadmium excretion in urine and feces in "normal" populations, and on the cadmium concentration in blood and urine of highly exposed ulations.

Preceding page blank

Introduction

Dependable analytical methods are of outmost importance in studies on health effects of environmental pollutants. Cadmium is of special significance in this respect, because of the low daily intakes estimated (250-350 µg) to induce the earliest effect, tubular dysfunction (1). The concentrations of cadmium commonly reported (1) in staple food like wheat and rice are below 0.1 µg/g wet weight. The concentrations corresponding to the critical daily intakes would be around 0.4 µg/g. Average urinary concentrations of cadmium among non-exposed persons are usually around 1 ng/g. In cadmium-exposed workers the levels may increase about 100 times. Urinary cadmium is an indicator of both body burden and cadmium-induced kidney damage.

The methods most commonly used for analysis of cadmium in staple food, and in urine, are atomic absorption spectrophotometry, neutron activation and the dithizone colorimetric method. The latter method is less sensitive than the two former, and is therefore nowadays not in common use for samples with low concentrations. The sensitivity of neutron activation or atomic absorption is dependent on the type of samples analyzed. Certain salts and metals will influence the analysis as discussed by Friberg et al., (1).

When analyses made in different laboratories are compared a poor agreement in results may be caused by analytical errors, failure to procure homogeneous subsamples or e.g. wall-effects in the storage of liquid samples. In the following study efforts were made to avoid systematical errors in the selection and storage of subsamples. The aim was to find possible differences in results of chemical analysis and not to explain from whence such differences emerge.

Materials

Grains

Two rounds of analysis were performed. In the first round five Swedish wheat samples and ten Japanese rice samples were analyzed. Two of these rice samples were so-called "standard rice", used for calibrating analytical methods within Japan. They are supplied by the National Institute of Public Health to laboratories upon request.

The wheat samples had been stored in glass bottles or paper bags until collection and then stored in transparent polyethene bags. From these batches 500 g samples were taken, from which sticks and straws were discarded. The samples were mixed by shaking thoroughly and subsamples were taken for the different laboratories. The rice samples had been stored in transparent uncolored plastic bottles.

The final data from each laboratory were sent to Dr. Jaroslav Vostal, Department of Pharmacology and Toxicology, University of Rochester, N.Y., U.S.A. No communication between the laboratories was permitted before Dr. Vostal produced a table of the comparison of data.

The second round of analysis included three Swedish wheat samples, one Swedish oats sample and one Japanese wheat sample from an air polluted area. The samples were stored and treated in a similar way as for the first round.

The coding of the second round was performed in a more elaborate way than that of the first round. The five samples were prepared from the original batches by the Karolinska Institute and given code numbers. Dr. Kazuo Nomiyama, Department of Hygiene, Jichi Medical School, Tochigi, Japan took six subsamples of each sample and gave them new codes. The key to the codes and all analytical results were sent directly by each laboratory to Dr. Vostal.

Urine

A pool of 10 liters of urine from 20 employees of the Karolinska Institute was thoroughly mixed and poured into six 1.5 liter bottles. Dr. Nomiyama added a standard solution of cadmium chloride to four of these bottles. A pool of 3 liters of urine from 6 workers occupationally exposed to cadmium in a Swedish Cd-Ni-battery factory was thoroughly mixed and poured into two 1.5 liter bottles. Another pool from 6 other workers, not so much exposed, was prepared in a similar way. From the total of ten 1.5 liter bottles so produced, subsamples were taken after shaking.

The original ten bottles were coded by the Karolinska Institute. Dr. Nomiyama divided the urines into subsamples and recoded them. Karolinska Institute recoded the subsamples once more before sending them to the participating laboratories. All codes and results were sent directly to Dr. Vostal. This procedure should assure a completely blind analysis.

Methods

Neutron activation analysis was performed by Isotope Technics Inc., Stockholm, according to a method originally described by Ljunggren et al., (2), which has now been modified. The sample is put in a quartz tube, sealed and irradiated in a nuclear reactor. The whole tube is crushed and washed in a vessel by a 10:1 mixture of HNO_3 and H_2SO_4 and then 20 mg Cd^{++} carrier and 20 mg Hg^{++} holdback carrier are added. The sample is wet digested in a Bethge apparatus with reflux until complete digestion. Several separation and precipitation procedures follow among which ion exchange is used for the final separation of Cd and Zn (Sjöstrand, unpublished data). From the eluate cadmium is precipitated on a thin gold plate by electrolysis (Sjöstrand, unpublished data) and the final measurement of the radioactivity is made in a scintillation detector. The recovery of the 20 mg of carrier - Cd, measured by weighing the plate (Sjöstrand, unpublished data), is usually about 60 %. The radioactive and stable Cd-ions are supposed to react chemically in exactly the same way.

In their work on wheat and rice, the Institute of Public Health, and Keio University Japan, used a simplified version of the standard method for cadmium analysis of rice, designated by the Japanese Ministry of Health and Welfare (3). The samples are ashed in a low temperature oven. The ash is treated with HNO_3 and this solution is analyzed by AAS, using a flame without background compensation. The standards are treated like the samples. For urine the Institute of Public Health used an atomic absorption method, employing extraction in dithizone/chloroform, which is the Japanese standard method (4). The standards are treated the same way as the samples throughout the whole process.

Karolinska Institute utilized an atomic absorption method for wheat and rice, in which the samples are prepared by dry ashing at 450°C, and dissolved in 1 M HNO_3. The analysis is performed with a heated graphite atomizer with deuterium background correction (5). For urine the Swedish laboratory used two different methods. Both employ regular atomic absorption after extraction in APDC/MIBK*. One method (the macromethod) uses sample volumes of about 100 ml. They are wet ashed, extracted and the final analysis is made with flame AAS on the organic phase. This is modified from Lehnert, Schaller and Haas (6). Keio University used a similar method for urine. The other method (micro-

* APDC = Ammonium pyrrolidinedithiocarbamate
MIBK = Methyl isobutyl ketone

method) at the Swedish laboratory is performed on 25 ml samples, and includes dry ashing, 1 M HNO_3 treatment and extraction in APDC/MIBK. The final analysis is made flameless on the organic phase with the heated graphite atomizer (Linnman, to be published).

Toyama Institute of Hygiene and Medical Microbiology used regular AAS after wet ashing and DDTC/MIBK* extraction for both wheat and urine. The Institute for Agricultural and Biological Sciences, Okayama University, analyzed the wheat samples with regular flame AAS after dry ashing at 450°C (Kobayashi, pers. comm.).

The Environmental Research Center, USA, contracted Stewart laboratories,Knoxville, Tennesee to make the analysis of wheat samples. The grains were powdered in a mechanical grinder equipped with a tungsten carbide blade. Two different analytical methods were employed for the powder. Method I involved digestion of the sample in H_2SO_4, dry ashing, packing the ash in a graphite tube and multielement determination with optical emission spectroscopy. In method II the powder was ashed over HCl in an O_2 atmosphere, the vapors condensed into the HCl in an ice bath, and the HCl solution was brought to a standard volume. Cadmium concentration in the HCl solution was determined with standard AAS.

The National Bureau of Standards chose the following method for wheat samples. Three to five gram samples were oxidized by wet ashing with nitric-perchloric acids after spiking with 10^{-7} g of ^{111}Cd and the excess acid was removed by evaporation. The residues were each taken up with 5 ml of 1.0 M HCl and passed through an anion exchange column (AG 1x8, 100-200 mesh) containing about 4 ml of resin. After washing the column with 25 ml of 1.0 M HCl, the Cd was eluted with 4 M HNO_3. When the eluates were evaporated to dryness, it was apparent that there was too much residue to spark directly so the Cd was electrodeposited onto gold wires. The altered isotopic ratios were measured by Spark Source Mass Spectrometry (SSMS). The preliminary results showed that sample C (wheat) was drastically underspiked so a second sample of about 0.8 g was taken and spiked with 2×10^{-7} g ^{111}Cd.

---

* DDTC = Dietyldithiocarbamat
MIBK = Methyl isobutyl ketone

Table 1. Comparison of cadmium analysis in wheat (1st round).
unit = ng Cd/g wet weight, duplicate analysis.

Sample No. (harvest year)	Laboratory Neutron activation range	average	Karolinska Institute, AAS range	average	Keio Univ. AAS range	average	Institute of Public Health, AAS average
P-1 (1945)	14- 24	19	24- 33	29	120-140	130	190
P-2 (1971)	71- 76	73	63- 75	69	160-180	170	160
P-3 (1970)	118-171	145	133-155	144	220-230	225	230
P-4 (1947)	28- 33	30	33- 35	34	120-150	135	120
P-5 (1971)	94-106	100	96- 97	97	180-220	200	170
Estimated variation coefficient = V	21.4 %		12.5 %		11.4 %	$V=100\sqrt{\frac{\Sigma\left(\frac{X_{i1}-X_{i2}}{\bar{x}}\right)^2}{2n}}$	

Results

AAS at the Institute of Public Health and Keio University gave values more than twice as high as those given by AAS at Karolinska Institute (Table 1). The difference is statistically significant ($p < 0.05$). There is, however, a very good agreement between the two Japanese laboratories, as well as between Swedish AAS and neutron activation. The estimated variation coefficient from duplicate analysis is 12.5% and 11.4 % respectively, for AAS at Karolinska Institute and Keio University, and 21.4 % for neutron activation.

The difference in analytical results between the Institute of Public Health and Karolinska Institute is similar in the first round of analysis of rice samples (Table 2).
Only one rice sample was analyzed with neutron activation, the result falling in between the Swedish and Japanese AAS results.

Table 2. Comparison of cadmium analysis in rice (1st round).
unit = µg Cd/g wet weight.

Sample No.	Laboratory			
	Karolinska Institute Individual values ; AAS	average	Neutron activation	Institute of Public Health AAS
R- 1[x]	0.079 0.081 0.089	0.083	0.130	0.19
R- 3	0.018 0.026	0.022		0.07
R- 4	0.025 0.028	0.027		0.07
R- 5	0.006 0.008	0.007		0.07
R- 6	0.029 0.031	0.030		0.11
R- 7	0.062 0.063 0.066	0.064		0.16
R- 8	0.109 0.113	0.111		0.26
R- 9	0.105 0.126	0.116		0.23
R-10	0.103 0.107	0.105		0.20

x = "standard rice, 0.2 µg/g".

Results of AAS at the National Institute of public Health and Keio University in round 2 (Table 3) differ more than 100 % from results of AAS at Karolinska Institute as well as neutron activation analysis. There is a good agreement between AAS at Karolinska and neutron activation, even though the AAS-values in the second

Table 3. Comparison of analysis of cadmium concentration in grains (2nd round).
Duplicate analysis when ranges are given. unit = ng Cd/g wet weight.

Laboratory		Sample No. (harvest year)				Estimated variation coefficient (V)
		1 (1971) wheat	3 (1945) wheat	4 (1971) oats	5 (1941) wheat	
Neutron activation	r	41 - 48	23 - 26	12 -17	22 - 22	14.1 %
	a	44.5	24.5	14.5	22.0	
Keio University	a	120	60	50	100	
Institute of Public Health	r	133 -144	67 -100		107 -111	16.5 %
	a	139	84	84	109	
Karolinska Institute	r	20.7- 40.6	17.1- 18.3	6.1- 7.2	14.5- 21.6	27.6 %
	a	30.7	17.7	6.7	18.1	
ERS, USA	a	220	53	210	65	
Toyama Inst. of Hygiene	r	44 - 51	32 - 36	20 - 21	23 - 28	9.8 %
	a	47.5	34.0	20.5	25.5	
Okayama University		44	33	17	79	
National Bureau of Standards	x	41	20	12	35	

r = range a = average

x = only one figure significant.

round are relatively lower than in the first round. AAS analysis at Toyama Inst. of Hygiene, at Okayama University as well as Spark source mass spectrometry isotope dilutions at National Bureau of Standards and neutron activation analysis generally showed a good agreement. There is a large variation in the data from the Environmental Research Center, USA and all values lie more than 100 % above the neutron activation values (Figure 1).

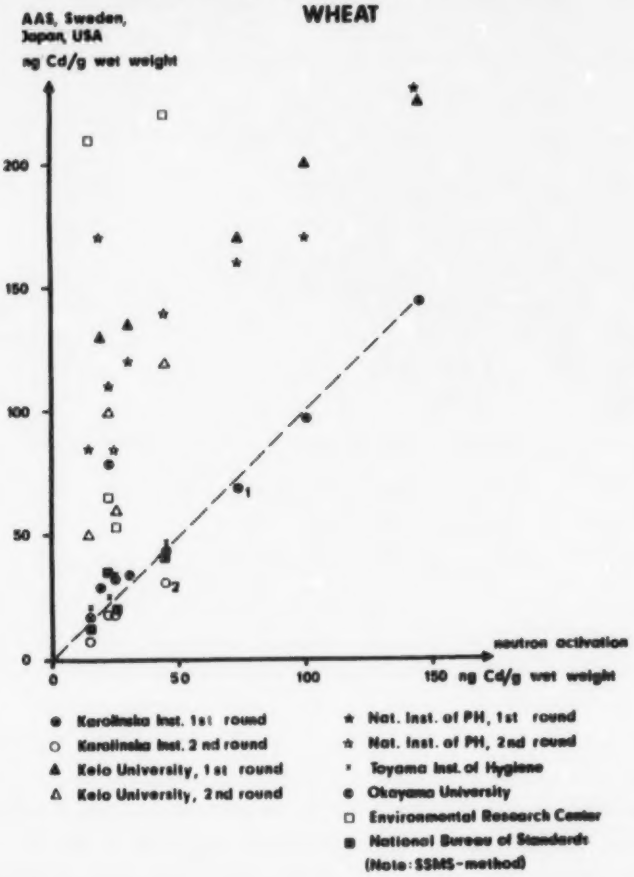


Figure 1. Comparison of cadmium analysis in wheat (1st and 2nd round). Neutron activation analysis used as a "reference method" on the abscissa and the ordinate is giving results of atomic absorption (and sparked source mass spectrometry isotope dilution) from all participating laboratories.

The results reported so far concern samples with concentrations 0.01-0.2 µg Cd/g, which is the range found in basic foodstuffs in non-polluted areas. Two samples from polluted areas with considerably higher concentrations were also compared (Table 4).

Table 4. Comparison of cadmium analysis of polluted wheat and rice.
unit = µg Cd/g wet weight.

Laboratory	Type of sample Wheat from Annaka, Japan individual values	 average	 Japanese "standard rice, 2 µg/g" individual values	 average
Neutron activation	2.95 2.71	2.83		
Karolinska Institute	2.54 2.59	2.57	2.11 2.32	2.22
Institute of Public Health	1.89 2.40	2.15		2.21
Keio University		3.20		
ERS, USA		2.58		
Toyama Inst. of Hygiene	2.94 3.20	3.07		
Okayama University		3.46		
National Bureau of Standards		1.6		
General average of all laboratories		2.68		
standard deviation		0.60		
variation coefficient		22.4 %		

The average of the results of analysis of wheat by 8 laboratories was 2.68 ug Cd/g (range 1.6 - 3.46 µg/g, variation coefficient 22.4 %). The systematic difference between the Institute of Public Health, Keio University and ERS, USA on the one hand and the remaining laboratories on the other hand as was seen in low-level samples did not occur for these higher-level samples.

As seen in Table 5 and Figure 2 there is generally a good agreement between the results of urine analysis apart from the two samples (A and D) with "normal" Swedish urine. Neutron activation gave 2 ug/liter and ≤ 0.8 µg/liter on duplicate subsamples. In the calculations of linear regression lines depicted in Figure 2, instead of ≤ 0.8 the number 0.5 was used. y = AAS µg Cd/liter, x = NA µg Cd/liter. The correlation coefficients between neutron

Table 5. Comparison of cadmium analysis of urine.
unit = μg Cd/liter.

Sample No. (Cd added μg/liter)	Laboratory Neutron activation	Keio University	Institute of Publ. Health	Karolinska Inst. micro	macro	Toyama Inst. of Hygiene
A (0)	2	1.0	1.0	0.6	0.2	0.43^{x}
D (0) = A	$\leq 0.8^{xx}$	1.1	1.9	0.3	0.2	0.35^{x}-1.8
B (12)	13	13.3	13.9	10.3	8.4	9.9
F (12) = B	13	12.5	13.2	10.4	8.4	9.95
C (20)	22	21.0	22.7	18.2	11.8	19.2
E (20) = C	18	22.4	20.2	18.1	14.0	19.75
Exposed workers						
G (0)	11	8.9	9.6	7.0	4.4	7.2
H (0) = G	7	8.6	8.6	7.1	5.8	7.65
I (0)	26	31.2	38.4	26.2	19.5	27.2
K (0) = I	28	28.7	29.7	25.1	18.0	29.75

x = flameless AAS, other method than the regular one used in Toyama.

xx = in our calculations the figure 0.5 is used.

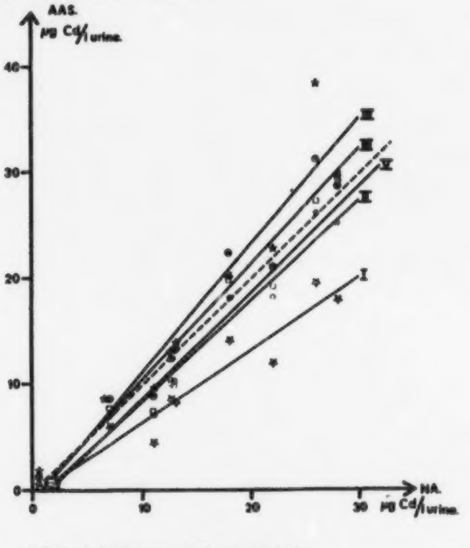


Figure 2. Comparison of cadmium analysis of urine. Neutron activation analysis used as a "reference method" on the abscissa and the ordinate is giving results of AAS from the five laboratories. Linear regression lines depicted.

activation analysis and AAS analysis at each laboratory vary between 0.96 and 0.98 (Table 6) and are all statistically significant ($p < 0.001$). Calculations were based on the average results of duplicate analysis. The slope of the regression line of AAS (macro-method) at Karolinska Institute was significantly less than 1 (at $p < 0.05$, $b = 0.69 \pm 0.14$). The Institute of Public Health had a relatively steep slope ($b = 1.21$) but it was not significantly higher than 1 (at $p < 0.05$, $b = 1.21 \pm 0.24$).

Table 6. Linear regression lines for comparison of neutron activation analysis and atomic absorption analysis of cadmium concentration in urine. Number of samples = 10. y = AAS value for each laboratory. x = neutron activation value.

I	Karolinska (macro)	$y = 0.69x - 0.62$	$r = 0.97$
II	Karolinska (micro)	$y = 0.96x - 1.18$	$r = 0.98$
III	Keio University	$y = 1.10x - 0.58$	$r = 0.98$
IV	Inst. of Publ. Health	$y = 1.21x - 1.11$	$r = 0.96$
V	Toyama	$y = 1.05x - 1.67$	$r = 0.98$

As the subsamples of urine used consisted of pairs of duplicate samples and some laboratories made duplicate analysis of each subsample, the repeatability of urine analysis can be calculated in two different ways (Table 7). In these calculations samples A and D were excluded.

Table 7. Estimated variation coefficient of cadmium analysis of urine (concentration range 7 - 30 μg/l).

Laboratories from which duplicate analysis of each subsample was reported:	Intrasample variation coefficient (8 duplicates)
Karolinska Institute	
micro-method	4.3 %
macro-method	12.0 % (7 duplicates)
Toyama Institute of Hygiene	3.2 %
Intersample estimated variation coefficient between 4 pairs of similar urine samples:	
Neutron activation	17.4 %
Karolinska Institute	
micro-method	1.6 %
macro-method	11.8 %
Keio University	4.5 %
Institute of Public Health	10.8 %
Toyama Institute of Hygiene	4.0

The recovery of added cadmium to samples B, C, E, and F varied between 60 and 100 % (Table 8).

Table 8. Relative recovery of added cadmium to urine samples. Assumed Cd concentration in original urine = 1.25 ug/liter. Averages of two subsamples.

Laboratory	ug cadmium added/liter urine 12	 20
Neutron activation	98.0 %	93.8 %
Keio University	97.4 %	102.1 %
Institute of Public Health	102.3 %	100.9 %
Karolinska Institute		
micro-method	78.1 %	85.4 %
macro-method	63.4 %	60.7 %
Toyama Institute of Hygiene	74.9 %	91.9 %

The recoveries agree with the slope of the linear regression lines calculated from all the samples.

Discussion

A methodological study on the Japanese standard method performed at the Institute of Public Health (3) showed a good agreement between low temperature ashing (average of 8 runs = 0.188 μg Cd/g, variation coefficient = 2.7 %) and APDC/MIBK extraction techniques (average of 8 runs = 0.189 μg Cd/g, variation coefficient = 7.4 %) when the same rice sample was analyzed. 9 different laboratories analyzed samples from this rice batch employing APDC/MIBK-extraction and the average concentration was 0.176 μg Cd/g with a variation coefficient of 10.2 %.

No detailed methodological study on the various steps in neutron activation analysis has been published. If the digestion of the irradiated sample is incomplete losses may occur. Sjöstrand (8) has described the wet digestion boiling reflux technique in detail and states that the distillation cycle is repeated until the solution is completely clear and colorless when boiling.

The AAS-method used at Karolinska Institute has been studied in detail (5) by addition of radioactive cadmium. The recovery was on an average 95 % with an average of 4.4 % losses in the second dry ashing step. The method was compared with neutron activation on 59 wheat samples ranging 29 to 257 ng Cd/g (7) giving a correlation coefficient of 0.946 and equation for linear regression AAS = 1.01 · NA - 1.65.

Also in the present study there was a good agreement between analysis of wheat by neutron activation and by AAS at Karolinska Institute as also by AAS at Toyama Institute of Hygiene and Okayama University and by SSMS at National Bureau of Standards. Keio University, Institute of Public Health and Environmental Research Center got systematically higher results. The lack of background correction after low-temperature ashing may explain the relatively high results from Keio University and Institute of Public Health. The great scatter of the results from Environmental Research Center make them hard to evaluate.

Similar systematic differences between Karolinska Institute, and Institute of Public Health can be seen for rice (Table 2). Further data on rice are now under processing with a larger number of samples analyzed by neutron activation. Rice and wheat have different composition of the ash, which may be of importance for the recovery of the various ashing procedures. No conclusion regarding analysis of rice will therefore be drawn at present.

Among the wheat samples analyzed one sample in the first round was also included in the second round. The results are included in Figure 1, marked with numbers 1 and 2. As can be seen, AAS at Karolinska Institute gave 77.5 ng Cd/g in the first round and 30.7 ng Cd/g in the second round. The same wheat batch harvested in 1971 had been analyzed with Swedish AAS in connection with another study and gave 42.5 ng/g, 50 ng/g, 51.5 ng/g and 56 ng/g (duplicate samples) (5). Neutron activation analysis gave values of 73 ng/g and 44.5 ng/g respectively on the same sample in the two rounds, Keio University, Japan, reporting 170 ng/g and 120 ng/g, and the Institute of Public Health 160 ng/g and 139 ng/g respectively. These consistent differences between the two sampling times indicate a real difference in cadmium concentration. This difference is distressing as the samples were taken from the same batch. On the other hand in the actual comparison between laboratories the subsamples were taken from samples on which cleaning and mixing had taken place. One way to limit the error in sampling from a large batch would be to grind the material and homogenize it. As our aim was to compare analysis of the original material used for studies on daily intake, that is the grains, we felt it would be more appropriate just to clean and mix the grains thoroughly before subsampling.

The systematic differences between Keio University, the Institute of Public Health and EPA, USA on the one hand and all other laboratories on the other hand which have been seen for low-level wheat samples are not seen for the wheat sample from a polluted area with a concentration around 2.7 µg/g. The results range about ± 30 % from the average. "Standard rice 2 µg/g" which had been analyzed by 10 laboratories in Japan (3) giving an average of 2.33 µg/g (variation coefficient 8.6 %) was again studied here giving 2.22 µg Cd/g at Karolinska Institute and 2.21 µg Cd/g at Institute of Public Health.

When the cadmium concentration in urine exceeds 5 µg/liter all AAS-methods used correlated well with neutron activation analysis. The macro-method at Karolinska Institute had systematic losses of about 30 %, which were statistically significant.

Methodological studies on the Japanese standard method for urine (dithizone/chloroform extraction) (9) show a good correlation between different laboratories. This method was also compared with APDC/MIBK extraction with a good agreement (r = 0.996). All samples were from a polluted area with cadmium concentrations ranging 2-26 µg/liter. The relative differences between results from different laboratories were larger at low concentrations.

The present study shows that there are problems in analyzing "normal" urine. None of the methods used can be looked upon as a good reference method. The same differences as found in grains between Keio University and the Institute of Public Health on the one hand and the other AAS laboratories on the other hand can be seen in urine findings. More methodological research is needed before cadmium content in normal urine can be analyzed with accuracy.

Conclusions

The findings in this study emphasize the need for international comparisons of trace metal analysis employing principally different methods. Such studies should give full disclosure of the methods used and any methodological studies performed earlier. A sufficient number of samples of the same type of material should be used in order that systematic differences can be evaluated. Efforts should be taken to assure blind analysis and randomization of sampling errors.

Only after such studies have been carried out is it meaningful to make comparisons e.g. average body burden, excretion or daily intake of metals in different countries.

Aknowledgements

We are grateful for the valuable assistance of Drs. Kobayashi, Kubota, LaFleur, Nomiyama, Shiroishi and Vostal.

References

1. Friberg, L., Piscator, M., Nordberg, G., and Kjellström, T., Cadmium in the environment, 2nd edition, Chemical Rubber Co. Press, Cleveland, 1974.

2. Ljunggren, K., Sjöstrand, B., Johnels, A.G., Olsson, M., Otterlind, G., and Westermark, T., Activation analysis of mercury and other environmental pollutants in water and aquatic ecosystems, IAEA-SM-142 a/22, p. 373-405, International Atomic Energy Agency, Vienna, 1971.

3. Yamagata, N., Iwashima, K., Kuzuhara, Y., and Yamagata, T., A model surveillance for cadmium pollution, Bull. Inst. Publ. Health, 20 (3): 170-186, 1971.

4. Japanese Ministry of Health and Welfare; The method for health examination of the inhabitants, a part of the provisional countermeasures against environmental pollution of cadmium; Report from the section for environmental pollution control, May 19, 1971 (in Japanese).

5. Kjellström, T., Lind, B., Linnman, L., and Nordberg, G., A comparative study on methods for cadmium analysis of grain with an application to pollution evaluation, Environmental Research (in press).

6. Lehnert, G., Schaller, K.H., and Haas, T., Atomabsorptionsspektrometrische Cadmiumbestimmung in Serum und Harn, Z. Klin. Chem. u. klin. Biochem., Vol. 6, 174, 1968.

7. Linnman, L., Andersson, A., Nilsson, K.O., Lind, B., Kjellström, T., and Friberg, L., Cadmium uptake by wheat from sewage sludge used as a plant nutrient source, Arch. Env. Health, 27, 45-47, 1973.

8. Sjöstrand, B., Simultaneous determination of Mercury and Arsenic in Biological and organic materials by activation analysis, Anal. Chem., 36, 814-819, 1964.

9. Japanese Association of Public Health, Research about the Standardisation of analytical methods for cadmium poisoning, Research Report 1970 (in Japanese).

THE DETERMINATION OF LEAD AND CADMIUM IN BLOOD BY ATOMIC ABSORPTION SPECTROSCOPY

H. T. DELVES

Hospital for Sick Children and Institute of Child Health, London
United Kingdom

ABSTRACT

The problems of matrix interferences that are encountered in the determination of lead and cadmium in micro-litre volumes of blood by discrete sampling flame and flameless atomization and atomic absorption methods are discussed. Procedures to overcome these interferences are given.

Preceding page blank

Introduction The determination of lead and cadmium in blood by conventional atomic absorption spectroscopy (AAS) requires pre-concentration from relatively large volumes of blood (1-5ml). However, these determinations may be carried out with only micro-litre volumes of blood if highly efficient atomization techniques such as discrete sampling flame atomizers (1),(2), or flameless atomization systems (3) are used. In order to achieve accurate analyses with these atomization techniques it is necessary to overcome matrix interferences and interferences from non-atomic absorption signals.

Experimental Analyses using the Delves-cup technique were carried out on a Perkin-Elmer '103' single beam instrument without continuum source background correction, and analyses with graphite tube furnace were made using a Perkin-Elmer '303' instrument fitted with a D_2 lamp background correction accessory. The graphite tube furnace was a modification, by Woolley (4) of that previously described by Alexander et al (5).

Blood-lead Analysis

Matrix interferences There was a 10% enhancement of sensitivity for blood-samples relative to aqueous standards with the Delves-cup method for blood-lead analysis. This presumably resulted from the occlusion of the lead in a volatile organic matrix. However, with the graphite tube furnace a depression of sensitivity was observed for the blood samples. In this latter technique the bulk of the organic matrix was removed during the ashing stage prior to atomization. The magnitude of the depression depended upon the power dissipated through the tube during the atomization stage i.e. tube temperature (Figure 1) and was constant at -16% within the power range 0.96 to 1.43kw.

The matrix interferences were overcome, with both techniques, by matching the matrix of the standard solutions to those of the blood samples. Multiple standard additions to a series of 10µl volumes of a single control blood sample were used with the flame sampling method, as previously

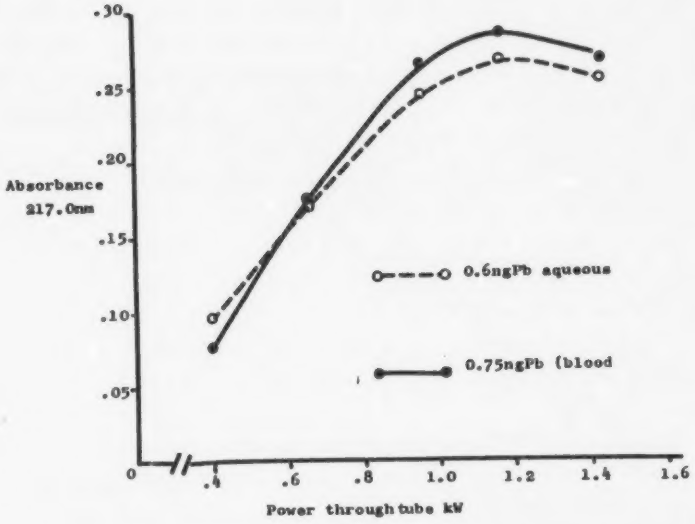


FIGURE I EFFECT OF BLOOD MATRIX ON THE FLAMELESS AA DETERMINATION OF LEAD (1µl SAMPLES)

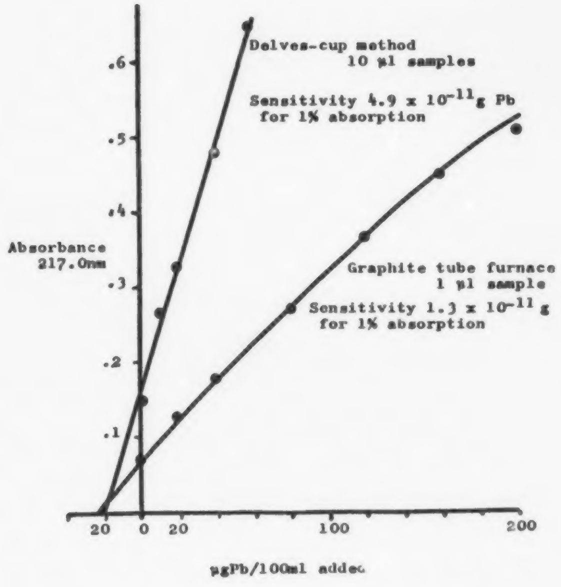


FIGURE 2 CALIBRATION CURVES FOR BLOOD-LEAD ANALYSIS

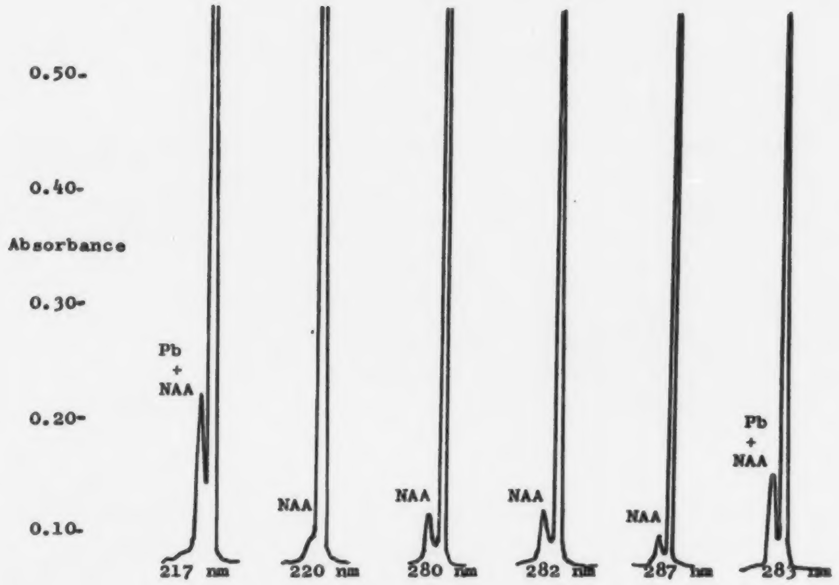
described (2). With the graphite tube furnace, a series of standards were prepared in a diluted blood matrix, by diluting 100µl of a control blood sample plus 100µl of an aqueous standard solution to 2.00ml with water. Calibration graphs for both techniques are shown in Figure 2.

Non-atomic absorption interferences arise from radiation scatter by solid particles and/or from molecular absorption by species that are volatilized simultaneously with the lead atoms. Unless these interferences are corrected for, the blood-lead analyses will be erronesouly high. There are three ways to correct for these interferences:

1. by using a continuum source (D_2 or H_2 lamp) background corrector,
2. by carrying out the analysis at a wavelength that is free from this interference (this may not always be possible)
3. by subtracting from the absorption signal obtained at the resonance line, the background absorption obtained at a nearby non-resonance line.

These procedures were investigated as follows:

Non-atomic absorption interferences with the Delves-cup method were investigated by making replicate determinations of lead in blood at the 283.3 and 217.0nm resonance lines and at nearby non-resonance lines. Representative results are shown in Figure 3. Two absorption signals were observed for each sample. The larger signal was due to radiation scatter by the combustion products of the sample and the smaller, which occurred when the sample had finished burning, was due to lead atoms plus any non-atomic absorption at the lead resonance lines (283.3nm, 217.0nm) and due to non-atomic absorption alone at the other non-resonance lines. There was no molecular absorption/light scatter at 220nm, which suggested that these interferences were also absent at 217.0 nm. There was however a variable non-atomic absorption signal from 280 - 287nm, which indicated molecular absorption rather than light scatter. The absorption signals due to species other than lead at 280, 282 and 287nm were found by replicate analysis to be equivalent to blood-lead concentrations at 283.3nm, of 6.3, 9.1 and 4.9µg/100ml



Pb = Pb atomic absorption signal
NAA = Non-atomic absorption signal

FIGURE 3 ABSORPTION SIGNALS AT RESONANCE AND NON-RESONANCE LINES IN BLOOD-LEAD ANALYSIS

respectively. Thus there would be a positive bias in blood-lead analysis by the above technique at 283.3nm unless this non-atomic absorption interference was eliminated. However, the above experiment did not indicate which of the three non-resonance lines could be used for background correction. The results in Figure 3 showed no detectable interference near the 217.0nm line and it was therefore concluded that any differences between blood-lead analyses obtained at 217.0nm and 283.3nm would be due to non-atomic absorption. 49 blood samples were analysed for lead at these two wavelengths. The results (Table I) showed that there was a positive bias of approximately 5μg/100ml at the 283.3nm line, which indicated that the correct non-resonance line to be used for background

TABLE I

NON-ATOMIC ABSORPTION IN BLOOD-LEAD ANALYSIS

49 blood samples with lead concentrations from 10-38µg/100ml analysed at 217.0nm and 283.3nm gave the following results:

Regression: µg/100ml

217.0nm = 283.3nm x 0.99 - 5.3

Correlation coefficient 0.93

Mean µg/100ml	S.D.	λ nm
24.2	6.4	217.0
24.4*	6.8	283.3

*5µg/100ml subtracted from each value.

correction was the 287nm line. These conclusions are supported by the work of Dawson et al (6) who used this 287nm line to provide continuous background correction for blood-lead analysis at 283nm by flameless atomization using a dual wavelength AA instrument.

Experiments with the graphite tube furnace and AA with continuous background correction showed that without background correction there was a significant positive error for blood-lead analysis at 283.3nm, but there was much less interference at the 217.0nm line. It is however recommended always to use background correction with flameless atomization systems for this analysis.

A comparison of blood-lead analysis by the two atomization techniques discussed is shown in Table 2. There was no significant difference between the results. The flameless technique was more sensitive (Figure 2), but the analysis rate was slower (40 tests per hour) than the discrete

TABLE II

COMPARISON OF BLOOD-LEAD ANALYSES

µg Pb/100ml

Cup tech.	G.T.F.	Cup tech.	G.T.F.
18	23	55	48
18	28	60	50
20	22	63	54
23	21	67	85
26	25	80	85
27	31	82	86
47	46	200	228

G.T.F. = Graphite tube-furnace AA method

sampling flame AA method (60 tests per hour) which was more suitable to routine analysis of large numbers of samples.

Blood-cadmium analysis

Solvent extraction and conventional flame AA, after wet ashing of 1 ml samples, allowed determinations to be made down to 0.2µg Cd/100ml. This procedure was however time-consuming and the new atomization systems were investigated for this analysis.

It was not possible to separate the cadmium absorption signals from those of the combustion products of the sample when using the Delves-cup technique, because of the relatively low vapour pressure of cadmium and its salts. Ediger and Coleman (7) have described a pre-ignition procedure for the removal of the matrix without loss of cadmium, but it was not possible to reproduce successfully their conditions or results, in this author's laboratory. Alternative oxidation procedures along the lines suggested by Cernik (8) are currently being investigated.

Preliminary work with the flameless atomization system has indicated that 3µl of blood are sufficient for the determination of cadmium. Because of the volatility of cadmium and its salts, precise control of the ashing stage and continuous background correction were found to be essential, to resolve the cadmium signals from those of the matrix. This method is still being developed.

Conclusion Matrix and non-atomic absorption interferences in the determination of lead and cadmium in blood are more severe with discrete sampling flame and flameless AA techniques than with conventional AA methods. However, these interferences may be overcome by suitable calibration and background correction procedures.

References

1 KAHN, H.L., PETERSON, G.E., "Atomic absorption microsampling with the 'sampling boat' technique", Atomic Absorption Newsletter, 7, 35,(1968).

2 DELVES, H.T., "A micro-sampling method for the rapid determination of lead in blood by atomic-absorption spectrophotometry," Analyst, 95, 431 (1970).

3 KIRKBRIGHT, G.F., "The application of non-flame atom cells in atomic-absorption and atomic-fluorescence spectroscopy," Analyst, 96, 609 (1971).

4 WOOLLEY, J.F., "The determination of iron and copper in high purity glasses by flameless AAS," Paper presented at the 4th International Conference on Atomic Spectroscopy, Toronto, Canada, November, 1973.

5 ALEXANDER, F.W., DELVES, H.T., REESON, R.B., "The application of atomic spectroscopy to the analysis of biological materials," 3rd International Congress of Atomic Absorption and Fluorescence Spectrometry, Paris, 1971, publ. Adam Hilger, London, p.44

6 DAWSON, J.B., ELLIS, D.J., FISHER, G.W., "A dual wavelength AA spectrometer for the determination of lead in blood," Paper presented at the 17th Colloquium Spectroscopicum Internationale, Florence, Italy, September, 1973.

7 EDIGER, R.D., COLEMAN, R.L., "Determination of cadmium in blood by a Delves cup technique," Atomic Absorption Newsletter, 12, 3,(1973).

8 CERNIK, A.A., "A preliminary procedure for the determination of cadmium in blood," Atomic Absorption Newsletter, 12, 163,(1973).

MESURE DU PLOMB DANS LES OS HUMAINS PROVENANT DE LA REGION PARISIENNE

L. JEANMAIRE, F. PATTI, N. CIALELLA, R. GROS

Commissariat à l'Energie Atomique, Département de Protection,
Service de Radiotoxicologie et Ecologie, Fontenay-aux-Roses,
France

RESUME

Cette étude a pour but l'obtention de données systématiques sur la teneur en plomb des os de personnes habitant la région parisienne. Les prélèvements sont faits pour obtenir des informations sur deux types d'os (côtes et vertèbres), sur les diverses classes d'âges et sur les deux sexes. Après minéralisation de l'os et concentration chimique le plomb est dosé par fluorescence X. Les résultats présentés correspondent à une centaine d'échantillons. On note généralement une concentration plus forte dans les vertèbres que dans les côtes et une augmentation en fonction de l'âge. Il est possible que les concentrations soient plus faibles chez les femmes que chez les hommes, mais l'échantillonnage actuel ne permet pas de l'affirmer. Ce travail n'est qu'une étape intermédiaire et doit être complété par de nouvelles mesures pour être réellement significatif de la contamination du plomb de la population parisienne.

ABSTRACT

The aim of this study was to obtain systematic data on the lead content of the bones of people living in the Paris area. Samples were taken to obtain information about two types of bones (ribs and vertebrae), various age categories and both

Preceding page blank

sexes. After mineralization of the bone and chemical concentration the lead was determined on the basis of X-ray fluorescence. The results obtained were for about a hundred samples. Generally speaking concentrations were higher in the vertebrae than in the ribs and increased with age. Concentrations may be lower in women than in men, but no proof of this was revealed in the sampling. This study only represents an intermediate stage in the investigation and must be completed by further measurements before it can be considered a really significant indication of the lead contamination of the population of Paris.

I. INTRODUCTION

Depuis 1962, le strontium 90 et le strontium stable des os humains sont dosés sur des prélèvements provenant de la région parisienne ; l'échantillonnage semble également adapté à l'étude d'autres éléments ; c'est pourquoi nous avons l'intention d'établir un bilan pour les plombs stables et radioactifs. Ce document ne présente que des résultats partiels concernant le plomb stable.

2. METHODE

Les échantillons sont des côtes et des vertèbres prélevées sur des sujets des deux sexes dont l'âge est compris entre 10 et 90 ans. Le mode de vie, la profession et la cause du décès sont inconnus.

Après dessiccation à l'étuve à 200°, les os sont calcinés au four en élevant progressivement la température de 400 à 700°. Chaque échantillon analysé est constitué par les cendres provenant de 1 à 5 prélèvements. Le plomb est entraîné sur un précipité d'oxalate, précipité avec un hydroxyde puis coprécipité sur un sulfate de strontium; le plomb contenu dans ce sulfate est alors mesuré par fluorescence X. Des essais ont montré qu'il n'y avait ni perte de plomb, ni contamination des échantillons durant la minéralisation.

Pour des teneurs en plomb supérieures à 10 µg par g de cendre, les essais de reproductibilités donnent des écarts type compris entre 6 et 8 %.

3. RESULTATS

La tableau I, indique les résultats en microgrammes de Pb par gramme de cendre pour environ 120 échantillons groupés en classes d'âge par décadres de 10 à 90 ans. Les remarques suivantes peuvent être faites.

3.1. Globalement les résultats sont extrêmement dispersés puisqu'ils vont de 5 à 150 µg.

3.2. En classant les résultats par nature, on constate que la teneur en plomb des vertèbres est généralement supérieure à celle des côtes. La valeur moyenne du rapport vertèbres sur côtes est égale à 1,2 environ.

3.3. Lorsque les résultats sont groupés par décade et par nature, il apparait une augmentation de la teneur en plomb en fonction de l'âge, jusqu'à 70 ou 80 ans. Par contre la classe la plus agée semble relativement moins contaminée. Même avec ce type de regroupement, les résultats de chaque classe sont très dispersés, l'écart type sur un résultat individuel étant fréquemment de 50 % ou plus. Entre 10 et 80 ans les droites représentant les concentrations en fonction de l'âge (t) exprimé en années, ont les formules suivantes, lorsqu'on les fait passer arbitrairement par 0 à l'origine : $C = 0{,}87\ t$ pour les côtes et $V = 1{,}03\ t$ pour

TABLEAU I - Teneurs en Pb par g de cendre d'os

ANS	Os	Nombre	Sexe	µg/g	Os	Nombre	Sexe	µg/g	Os	Nombre	Sexe	µg/g	Os	Nombre	Sexe	µg/g	Os	Nombre	Sexe	µg/g
10 - 19	C	2	F	11	V	2	F	17	C	1	M	10	C	1	F	8	V	1	F	12
	C	1	M	6	V	1	M	6	C	1	M	10	V	1	M	10	C	2	M	8
	V	2	M	7	C	2	F	13	V	2	F	14	C	1	F	7	V	1	F	12
	C	1	M	12	V	1	M	9	C	1	M	8	V	1	M	14	C	1	F	6
	V	1	F	11	C	2	M	7	V	2	M	11	C	1	M	16	V	1	M	17
20 - 29	C	2	M	25	V	2	M	34	C	2	M	44	V	2	M	52	V	3	M	12
	C	3	M	13	C	1	M	12	C	3	M	9	V	3	M	20				
30 - 39	C	3	F	25	C	2	F	17	V	2	F	26	C	2	F	37	C	2	M	45
	V	2	M	39	V	1	F	22	C	1	M	18	V	1	M	19	C	1	F	15
	C	2	M	21	V	2	M	82	C	2	F	24	V	2	F	36				
40 - 49	C	2	M	5	V	2	M	14	C	2	M	83	V	2	M	122	C	3	F	36
	V	3	F	69	C	2	F	27	C	2	M	65	C	3	M	101	V	2	M	38
	C	2	F	29	V	2	F	33	C	3	M	27	V	3	M	22	C	2	M	42
	V	2	M	64																
50 - 59	C	3	F	37	V	3	F	51	C	2	M	13	V	2	M	44	C	2	M	20
	V	2	M	24	V	3	M	32	C	3	M	54	C	4	M	43	V	4	M	42
	C	1	M	67	V	1	M	95	C	2	M	57	V	2	M	81	V	3	F	75
60 - 69	C	3	M	42	C	3	F	23	V	2	M	41	C	2	M	40	C	4	M	57
	V	4	M	73	C	2	M	120	V	2	M	107	C	1	M	93	V	1	M	93
	C	3	M	60	V	3	M	59												
70 - 79	C	5	F	28	V	5	F	39	C	4	F	62	V	4	F	74	C	3	M	56
	V	3	M	67	C	3	M	57	C	2	M	33	V	2	M	44	V	3	M	83
	V	3	M	84	C	3	M	147	C	4	F	91	C	3	M	54	C	3	M	40
	V	4	M	71	V	3	M	79	C	4	M	68	C	3	M	61				
80 - 89	C	2	F	30	V	2	F	34	C	3	M	33	V	3	M	43	C	4	F	26
	V	4	F	31	C	2	M	28	V	2	M	40	C	2	F	30	C	1	M	65
	V	1	M	99	V	1	F	72	C	1	F	46	C	1	F	54	C	1	F	105
	C	1	F	30																

Légende os C = côte V = Vertèbre
NB = Nombre de prélèvements dans l'échantillon.

les vertèbres. Ces valeurs sont supérieures à celles données par Holtzman et al. (1), Schroeder et Tipton (2), Horiuchi et al. (3) qui trouvent une pente de l'ordre de 0,5 à 0,6.

L'interprétation de valeurs très dispersées est toujours délicate et doit rester prudente ; une analyse statistique même très complète, ne comble pas les lacunes provenant d'un échantillonnage insuffisant.

En considérant les résultats de 10 à 80 ans on note une augmentation de la teneur en plomb en fonction de l'âge ; cet accroissement continu indique que l'état d'équilibre n'est pas encore atteint à 80 ans ; dans ce cas, entre 80 et 90 ans, les valeurs inférieures, ne peuvent s'expliquer que si l'échantillonnage de cette classe d'âge est insuffisamment représentatif ou différent de celui des classes précédentes.

En ne prenant que les résultats de 40 à 90 ans, on peut admettre soit un passage par un maximum à 70-80 ans (cas identique au précédent), soit l'existence d'un plateau à 50 µg environ, qui serait mal défini par suite d'un échantillonnage insuffisant ; dans ce cas l'état d'équilibre avec le milieu serait atteint.

3.4. Dans chaque classe d'âge, les valeurs moyennes trouvées chez les femmes sont plutôt inférieures à celles trouvées chez les hommes.

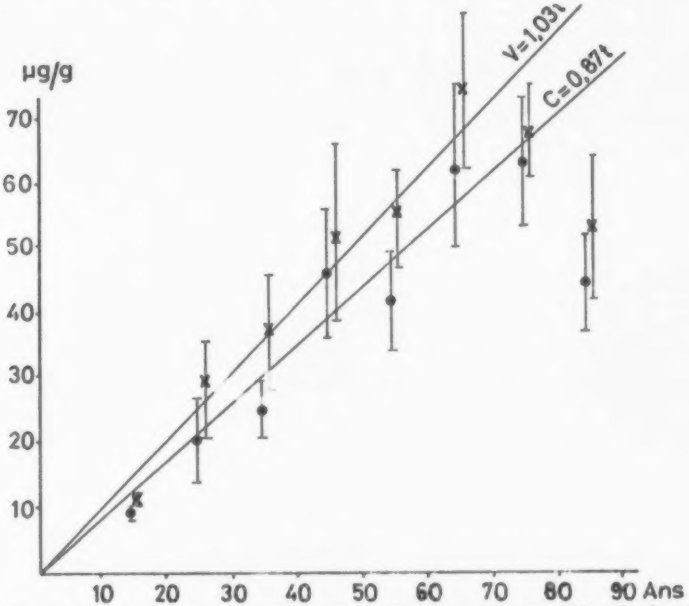


Fig.1 . Evolution de la teneur moyenne en Pb dans les vertèbres ✕ et dans les côtes ● en fonction de l'âge. Les échantillons sont groupés par décade. Les barres d'erreur correspondent à l'écart type sur la valeur moyenne.

4. CONCLUSION

La dispersion des valeurs trouvées, les différences notées en fonction de la nature de l'os, de l'âge des sujets et de leur sexe, sont telles qu'il y a lieu de continuer l'étude entreprise pour lui donner une assise solide, sans ambiguité.

Remerciements : Nous remercions Madame M.Garcet, et Mademoiselle J. Laporte de leur collaboration technique efficace.

REFERENCES

(1) HOLTZMAN, R.B., LUCAS, H.F. Jr, ILCEWICZ, F.H. - The concentration of lead in human bone, Argonne National Laboratory report ANL - 76 15 (1968) 43-49.

(2) SCHROEDER, H.A., TIPTON, I.H., The human body burden of lead, Arch. Environ. Health 17, 965-968 (1968)

(3) HORIUCHI, K. HORIGUCHI, S. SUEKANE, M. - Studies on the industrial lead poisoning - the lead contents in organ tissues of the normal Japanese, Osaka City Med. Journal 5, (1), 41-70 (1959).

ZUR BLEI- UND CADMIUMANALYTIK IN BIOLOGISCHEN MATRICES

M. STOEPPLER[+], F. BACKHAUS[+], R. DAHL[+],
M. DUMONT[++], H. HAGEDORN-GÖTZ[+], K. HILPERT[+],
P. KLAHRE[+], H. RÜTZEL[+], P. VALENTA[+], H. W. NÜRNBERG[+]

+ Zentralinstitut für Analytische Chemie der Kernforschungsanlage Jülich GmbH, BRD

++ Ecole des Hautes Etudes Industrielles, Lille, France

KURZFASSUNG

Es wird über Arbeitstechniken und Erfahrungen bei der Probenahme sowie über Aufschlussmethoden berichtet. Weiter werden die eingesetzten Verfahren: flammenlose Atomabsorptionsspektrometrie (auch mit automatischer Probeneingabe), Pulse-Polarographie und Isotopenverdünnungs-Massenspektrometrie beschrieben. Abschliessend werden Messergebnisse für Pb und Cd in Bovine Liver, Blut-, Urin- und Haarproben - teilweise auch im Methodenvergleich - mitgeteilt und diskutiert.

ABSTRACT

The paper deals with sampling techniques and experience, and decomposition methods. It also describes the processes used in flameless atomic absorption spectormetry (including the method using automatic insertion of samples), pulse polarography and isotope dilution mass spectrometry. Finally, the results of lead and cadmium measurements in bovine liver, blood, urine and hair samples are reported and discussed - with a comparison of methods in some cases.

EINLEITUNG

Da sich das Ausmass von Intoxikationen durch Elemente wie Blei, Cadmium und Quecksilber ebenso aus klinischen Befunden wie aus spurenanalytischen Daten ergibt, ist die Frage richtiger Analysenwerte hier sehr wichtig.

Man weiss jedoch aus einer Reihe von Vergleichsprogrammen, dass bei Spurenanalysen erhebliche Abweichungen vom wahren Wert auftreten (1,2,3), und dass kritische Studien der Analysenmethoden mit dem Ziel einfachere, standardisierte Verfahren mit grösserer Zuverlässigkeit zu bekommen, notwendig ist.

In der Kernforschungsanlage Jülich werden im Rahmen des von der Bundesregierung geförderten Umweltprogramms der Grossforschungsanlagen der Bundesrepublik Deutschland solche Studien durchgeführt. Wir untersuchen für eine Reihe von Elementen die Probenvorbereitung, Aufschluss- und Bestimmungsmethoden sowie Möglichkeiten zur Automatisierung der flammenlosen Atomabsorptionsspektrometrie und der Pulse-Polarographie. Ueber bisherige Erfahrungen bei der Bestimmung von Blei und Cadmium in Blut, Urin, Organproben und Haaren soll hier zusammenfassend berichtet werden. An anderer Stelle wurden kürzlich Messwerte für Blei in Biomatrices (4) sowie von Blei, Cd und As in Oberflächenwasser, Mineralwasser, Meerwasser und einer Reihe von Nahrungs- und Genussmitteln (5) mitgeteilt.

EXPERIMENTELLES

Probenahme und Probenvorbereitung

Bei Spurenbestimmungen ist die Probenahme und die Probenvorbereitung sehr viel sorgfältiger als bei der klassischen Analyse durchzuführen. Man muss daher ebenso auf ausreichende Einwaage der weitgehend homogenisierten Probe wie auf Vermeidung von Einschleppungen der gesuchten Elemente (Kontamination) und Verluste durch Adsorption an Gefässwände etc. bei der Probenvorbereitung achten.

Bei Blutproben verwenden wir zur Entnahme stets auf Pb bzw. Cd geprüfte Behältnisse, die mit Antikoagulantien (EDTA, Heparin, Citrat) versehen sind.

Aliquots der Blutproben werden entweder direkt nach der Entnahme in ein

TABELLE I

AUFSCHLUSSMETHODEN ZUR SPURENELEMENTBESTIMMUNG MIT DER FLAMMENLOSEN AAS, DER PULSE-POLAROGRAPHIE UND DER ISOTOPENVERDUENNUNGSMASSENSPEKTROMETRIE

METHODE	max Menge	Zeitdauer	Bemerkungen
Muffeloefen	10 g	bis 100h	Einfach, aber zeitraubend, im ppb-Bereich mit Vorbehalt
Spezialoefen	1 kg	bis 100h	Aufwendig, aber bei Nahrungsmitteln bisweilen unumgänglich. Nicht für alle Elemente und im ppb-Bereich günstig
Mikrowellenveraschung	50 g	bis 100h	Sehr schonend, da max. Temp bei 200°C Kontaminationsvorsorge möglich. Nahezu vollständige Mineralisierung, daher besonders für Pulsepolarographie und MS geeignet Trotz hoher Gerätekosten bei grossen Probenzahlen günstig
HNO_3 unter Druck	1 g	bis 4h	Zahlreiche Varianten möglich, mit Einwaagen von 1 mg bis 1 g. Relativ rasch und wegen des geringen Säurebedarfs auch im allgemeinen kaum Kontaminationgefahr. Varianten zur halbautomatischen Probenvorbereitung möglich. Trotz klarer Lösung keine vollständige Mineralisierung, daher kaum für P.P. und MS brauchbar

TABELLE I (Fortsetzung)

METHODE	max. Menge	Zeitdauer	Bemerkungen
HNO_3 in der Gasphase	1 g	bis 30 min	Sehr rasch und fast frei von Kontamination. Aufwendig und für Serienbestimmungen in der derz. Form ungeeignet. Trotz klarer Lösung keine vollständige Mineralisierung, daher nicht für P.P. und MS geeignet
Fe^{+3}/H_2O_2	1 kg	bis 20 h	Für begrenzte Probentypen hervorragend geeignet. Kontamination im allgemeinen gering
Nassaufschlüsse: $H_2SO_4/HClO_4$ H_2SO_4/HNO_3 $HClO_4/HNO_3$	bis 5 g	bis 5 h	im allgemeinen bei mittleren Einwaagen und flüssigen Proben günstig. Vor allem für die Pulse-Polarographie brauchbar. Kontamination nicht vernachlässigbar Bei Verwendung von Perchlorsäure sind Spezialabzüge und besondere Sicherheitsvorkehrungen nötig $HClO_4$ ist für die flammenlose AAS ungeeignet

Aufschlussgefäss überführt oder - für die flammenlose AAS-in Polyolefingefässen (z.B. Eppendorf-Reaktionsgefässen) mit penta-destilliertem, praktisch schwermetallfreiem Wasser hämolysiert. Unter diesen Bedingungen ist eine Kontamination durch Blei und Cadmium aus dem Gefässmaterial minimal und in der Regel vernachlässigbar.

Urinproben werden in mit HNO_3 oder HCl gereinigten und auf Pb geprüften Polyäthylenfläschchen gesammelt und zur direkten Analyse entweder in ebenfalls vorgereinigte Eppendorfgefässe überführt und angesäuert oder in eine polarographische Zelle eingebracht. Auch hierbei ist eine merkliche Kontamination nicht zu beobachten. Bei Organ- und Haarproben liegen Pb- und Cd-Gehalte im ppm-Bereich vor, so dass im allgemeinen bei Einsatz der beschriebenen Gefässe und ausreichender Einwaage die Kontaminationsgefahr gering ist. Bei Haaren ist der Waschvorgang vor der Bestimmung problematisch. Auf die umfangreichen Arbeiten hierzu wurde an anderer Stelle hingewiesen (6,7).

PROBENAUFSCHLUSS

Unsere bisherigen Erfahrungen mit verschiedenartigen klassischen und moderneren Aufschlussmethoden sind in Tabelle 1 zusammengefasst. Ein detaillierter Bericht hierüber, in dem auch eine von uns entwickelte Mikrovariante des HNO_3-Druckaufschlusses beschrieben ist, wird zur Zeit vorbereitet (8).

KONTAMINATIONSPROBLEME

Es wird, falls erforderlich, in sog. clean benches oder unter streng kontrollierten Bedingungen und mit hochreinen (z.B. Suprapur ®) Reagentien gearbeitet, um eine Kontamination von aussen zu vermindern. Als günstigste Materialien für Aufschluss- und Bestimmungsgefässe erwiesen sich spanabhebend bearbeitetes Teflon und synthetischer Quarz (z.B. Suprasil®), die nach Behandlung mit hochreinen Säuren sehr niedrige Blindwerte ergaben.

METHODEN UND GERAETE

ATOMABSORPTIONSSPEKTROMETRIE (AAS)

Bei unseren Untersuchungen wurde überwiegend die erst seit 1970 kommer-

TABELLE II

FLAMMENLOSE ATOMABSORPTIONSSPEKTROMETRIE

GERÄTEDATEN:

Fisher-Jarrell-Ash 810, Zweikanal, Vierstrahl
Perkin-Elmer 300, Einstrahl mit Deuteriumkompensator
Perkin-Elmer Graphitküvetten: HGA 70/72/74 + Rossimat
ANALYSENLINIEN: Pb 283.3 nm, Cd 228.8 nm

NACHWEISGRENZEN (für 50 µl Probeneingabe)

Pb: wäßrig $1 \cdot 10^{-11}$g (0.2 µg/L) Blut/Aufschlußlsgg: $1 \cdot 10^{-10}$g
Urin: $5 \cdot 10^{-10}$g

Cd: wäßrig $1 \cdot 10^{-12}$g (0.02 µg/L) Blut/Aufschlußlsgg: $1 \cdot 10^{-11}$g

MATRIXPROGRAMME:

Pb in hämolysiertem Blut:

Trocknen	bis	95°C	60	sec
Zersetzen I		250°C	60	"
Gleitprogramm		640°C	72	"
Atomisieren		2400°C	5	"
Abkühlen			30	"

Blei in Aufschlußlsgg./Urin

Trocknen	bis	95°C	60	sec
Zersetzen	bis	300°C	30	"
Atomisieren		24oo°C	5	"
Abkühlen			30	"

Cd in hämolysiertem Blut:

Trocknen	bis	95°C	60	sec
Zersetzen I		250°C	30	"
Gleitprogramm		400°C	180	"
Atomisieren		1800°C	5	"
Abkühlen			30	"

Cd in Aufschlußlsgg. etc.

Trocknen	bis	95°C	60	sec
Zersetzen		300°C	30	"
Atomisieren		1800°C	5	"
Abkühlen				

TABELLE III

DATEN ZUR PULSE-POLAROGRAPHIE

Methode: Anodic Stripping (Inverspolarographie), Elektrolysedauer 2 min

Gerät: PAR (Princeton Applied Research) 174

NACHWEISGRENZEN: (minimales Volumen 4 ml)

Element	in wäßrigem Medium	in Aufschlußlösungen/Urin
Cadmium	ca 0.2 ppb	ca 0.5 - 1 ppb
Blei	ca 0.2 ppb	ca 0.5 - 1 ppb

Relative Standardabweichung 2 - 10% (matrixabhängig)

Probenvorbereitung: Außer beim Urin ist in allen Fällen von biologischen Proben ein Aufschluß notwendig. Mit gutem Erfolg ist der Mikrowellenaufschluß und auch der nasse Aufschluß mit $H_2SO_4/HClO_4$ anwendbar.

Kontaminationsgefahr durch die Aufschlußgefäße und ggf. durch Leitsalze

TABELLE IV

ISOTOPENVERDÜNNUNGS-MASSENSPEKTROMETRIE

GERÄTEDATEN:

Varian-MAT CH-5 mit Thermionenquelle

Isotopenverhältnis: ^{204}Pb (Spike)/natürliche Isotope

NACHWEISGRENZEN, FEHLERBEREICH:

absolute Nachweisgrenze ca $5 \cdot 10^{-9}$g

relativ abhängig von der Probenmenge

Rel. Standardabweichung im günstigsten Bereich <1%, an der Nachweisgrenze im Prozentbereich

PROBENVORBEREITUNG:

Aufschluß (günstig: mit Mikrowellen)

Lösen, ggf. Abtrennung von Matrixbestandteilen

Anodische Abscheidung des Pb

Auflösen in wenig HNO_3, Aufbringen auf mit SiO_2-Phosphorsäure imprägniertes Verdampferband

Kontaminationsgefahr bei allen Schritten ziell verfügbare flammenlose Variante eingesetzt, da sie gegenüber der AAS mit Flamme den Vorteil der grösseren Empfindlichkeit und gegenüber der Pulse-Polarographie den der höheren Analysenfrequenz besitzt.

Derzeit wird ein von Perkin-Elmer, Deutschland, nach Arbeiten von Pickford und Rossi (9) gebauter Prototyp zur automatisierten Probeneingabe in Graphitküvetten (Rossimat) in Jülich erprobt.

Wir hoffen, damit neben einer weiteren Steigerung der Analysenfrequenz eine im Vergleich zur Handdosierung um mindestens Faktor 2 bessere Reproduzierbarkeit zu erreichen.

Tabelle II fasst die wichtigsten Daten der eingesetzten Gerätekombination und die Temperaturprogramme zur direkten Bestimmung von Pb und Cd in Blut und Urin sowie in Aufschlusslösungen von Körperorganen und Haaren zusammen.

PULSE-POLAROGRAPHIE (P.P.)

Diese, 1958 von Barker erstmals beschriebene Methode (10) erzielt vor allem in Kombination mit dem sog. anodic-stripping-Prinzip (Inverspolarographie) wegen ihres günstigen Signal-Rausch-Verhältnisses sehr niedrige Nachweisgrenzen.

Ausser Urin, der direkt analysiert werden kann, ist bei den übrigen Matrices stets ein Aufschluss erforderlich (vgl. Tab. I).

Vorarbeiten zu einer Teilautomatisierung haben ebenfalls in Jülich begonnen.

Tabelle III zeigt die Daten dieser in zunehmendem Umfang in der Umweltanalytik gebräuchlichen Methode.

ISOTOPEN-VERDUENNUNGS-MASSENSPEKTROMETRIE

Zur Beurteilung der Richtigkeit von Spurenanalysen ist es wünschenswert, für jedes interessierende Element noch eine dritte Methode einsetzen zu können. Vor allem bei dem mit nuklearen Methoden im extremen Spurenbereich praktisch nicht bestimmbaren Blei bietet sich die Isotopen-Verdünnungs-Massenspektrometrie als zusätzliche Möglickeit neben AAS und P.P. an.

Tabelle IV bringt Daten dieser - gegenwärtig in Jülich in der Enderprobung befindlichen Methode.

TABELLE V

Bestimmung von Pb und Cd in NBS Bovine Liver

NBS-WERTE:		
Pb	0.34 ± 0.08 ppm	
Cd	0.27 ± 0.04 ppm	
KFA/ZAC:		
Pb mit AAS	0.32 ± 0.09 ppm[1]	n = 20
	0.33 ± 0.08 ppm[2]	n = 22
Pb mit Pulse-Pol.	0.38 ± 0.04 ppm[3]	n = 6
Cd mit AAS	0.25 ± 0.06 ppm[4]	n = 10
Cd mit Pulse-Pol.	0.21 ± 0.04 ppm	n = 6
BEMERKUNGEN:	[1] Druckaufschluß, Einw. > 200 mg [2] Mikroaufschluß, Einw. ca 10 mg [3] Pb-Kontamination beobachtet [4] Kontamination nicht unmöglich	

TABELLE VI

Blei im Blut (Werte in µg/100ml Vollblut)

Kontrollgruppe	Männer	Frauen	Mittelwert	Range
A (z=64)	12.8 (z=36)	10.4 (z=28)	11.8	4 - 27
B (z=65)			13.7	6 - 31
C (z=5)			22.0	12 - 27
D (z=40)	23.2 (z=20)	14.4 (z=20)	18.8	8 - 120
E (z=26)	20.9		20.9	9 - 40

Erläuterungen: Gruppen A und B unbelastete Kollektive
Gruppen C und E nachweislich bleibelastet
Gruppe D externer Vergleich, vermutlich mit Anteil an belasteten Personen

TABELLE VII

Vergleichsmessungen zwischen flammenloser AAS und Pulse-Polarographie (anodic stripping) Werte in ppb

BLUTPROBEN			URINPROBEN		
AAS	Polarographie		AAS	Polarographie	
205	270		115	110	
75	28		20	47	
365	405		20	86	
145	125	$\frac{PP}{AAS} = 1.08$	50	65	$\frac{PP}{AAS} = 1.50$
400	415		70	65	
184	285		55	60	
695	720		20	95	
230	225		20	25	
80	70				
145	65				
345	485				
261	281		46	69	

TABELLE VIII

GERÄTEVERGLEICH DURCH MESSUNG VON 6 BLUTPROBEN (Werte in ppb)

Probe	I	II	III	IV	Mittelwert
1	370	240	370	270	312±67 (21%)
2	240	180	190	190	200±27 (13%)
3	130	110	130	150	130±16 (12%)
4	480	330	370	280	365±53 (15%)
5	200	110	180	180	167±37 (22%)
6	630	610	640	630	627±13 (2%)
Mittel	340	263	310	283	Gesamt-Ø 299±33 (11%)

Erläuterungen:

I Jarrell-Ash 810/I am 05.04.74 mit HGA 72

II Perkin-Elmer 300 am 08.04.74 mit HGA 74

III Jarrell-Ash 810/I am 11.04.74 mit HGA 72

IV Jarrell-Ash 810/II " "

Bei bisweilen beträchtlichen Abweichungen in Einzelfällen liegen die Mittelwerte der Pulse-Polarographie - eventuell kontaminationsbedingt - bei Blutblei nur unwesentlich, bei der direkten Bleibestimmung in Urin allerdings merklich höher. Im letzteren Fall könnte einerseits die Grenze der Möglichkeiten der direkten flammenlosen AAS erreicht sein, andererseits eine Störung durch Sn bei der Polarographie vorliegen.

Wenn man davon ausgeht, dass zumindest im Blut die direkte Bestimmung mit der flammenlosen AAS brauchbare Mittelwerte liefert, so überraschen doch beim Vergleich von Einzelproben zwischen AAS und Polarographie und auch zwischen Labors, die die flammenlose AAS anwenden, Werte, die nicht selten um mehr als den Faktor 2 differieren.

Wir haben daher versucht, dies durch Vergleichsmessungen unter Routinebedingungen zu studieren. Dazu wurden identische Blutproben an drei verschiedenen Geräten sowie eine Blutprobe über einen längeren Zeitraum am gleichen Gerät gemessen.

Tabelle VIII fasst die Pb-Messungen in den Blutproben zusammen. Die Unterschiede zwischen den einzelnen Geräten erreichen bei Einzelwerten bisweilen fast den Faktor 2, während sich die Mittelwerte meist nicht so beträchtlich unterscheiden. Dennoch sind auch hier die Schwankungen merklich.

Im Langzeittest mit einem Jarrell-Ash 810 wurde in vier Blutproben im Verlauf von 11 Tagen arbeitstäglich der Pb-Gehalt nach jeweils neuer Entnahme eines 50-100 μl-Aliquots und Hämolyse bestimmt, wobei jeweils n=5 Parellelmessungen durchgeführt wurden.

Aus Tabelle IX ist zu erkennen, dass die Langzeitstandardabweichungen beträchtliche Werte erreichten.

Um zwischen gerätebedingtenMesswertschwankungen und Einflüssen der Blutmatrix differenzieren zu können, wurden 100 im gleichen Zeitraum durchgeführte Kontrollmessungen mit einer schwach sauren 0.02 ppm-Pb-Eichlösung zusätzlich ausgewertet. Die Standardabweichung des Mittelwertes dieser Messungen lag bei 10%, so dass man einen Einfluss der Matrix nicht ausschliessen kann. Dennoch deuten die beträchtlichen Abweichungen bereits bei wässrigen Eichlösungen - Tag zu Tag-Abweichungen sollten dabei im allgemeinen 5% nicht übersteigen - auf Instabilitäten hin, die entweder

TABELLE IX

Langzeitmessungen von vier Blutproben, Werte in ppb
GERÄT: Fisher-Jarrell-Ash 810 mit Graphitküvette HGA 72

Tag	Probe 1	Probe 2	Probe 3	Probe 4	Tagesmittel
Mo	275	320	340	370	326
Di	230	310	310	410	315
Mi	220	240	270	520	312
Do	200	310	350	430	322
Fr	180	270	300	350	275
Mo	340	350	360	500	387
Di	210	290	160	360	255
Mi	270	320	220	410	305
Do	230	260	250	390	282
Mittel	240±50 (21%)	300±40 (13.3%)	280±70 (25%)	420±60 (14.3%)	308±36 (11.7%)

TABELLE X

Bleibestimmungen in Haaren nach Mikrodruckaufschluß
Methode: flammenlose AAS, Eingabe in 0.5 M HNO_3

Probandenzahl 30, unbelastet, Einwaage 10-20 mg
männlich (z=15) Mittelwert 8.8 ppm, Range 2.2 - 39 ppm

weiblich (z=15) Mittelwert 6.2 ppm, Range 0.2 - 15 ppm

TABELLE XI

Cadmiumbestimmungen im Blut, Direkteingabe von
1 + 15 mit pentadest. Wasser hämolysiertem Blut in die
HGA 72, kombiniert mit J.A. 810. Programm siehe Tab.2
Probandenzahl: 37, keine besondere Belastung bekannt,
keine Differenzierung zwischen Männern und Frauen

Mittelwert: 9.5 ppb Range 4-19 ppb

MESSERGEBNISSE, DISKUSSION

Die mit Blut, Urin, Bovine Liver und Haaren durchgeführten Messungen zur Ermittlung von Pb- und Cd-Gehalten dienten zunächst vor allem dem internen und externen Methodenvergleich, um zu einer ersten Abschätzung der Richtigkeit dieser Bestimmungen zu kommen.

Tabelle V fasst die Ergebnisse für Pb und Cd in NBS 1577 Bovine Liver zusammen. Der gegenüber der AAS höhere Wert der Pulse-Polarographie für Pb könnte auf Kontamination beruhen, der recht niedrige für Cd ist überraschend, aber durch hinreichend viele Messungen gesichert; er soll trotzdem noch einmal überprüft werden.

Zur Ermittlung des Blutbleigehalts unbelasteter Personen im Raume Aachen/Jülich wurden 1973/74 zwei Kollektive mit der flammenlosen AAS untersucht. Es ergaben sich - im Verhältnis zu bisher angenommenen Mittelwerten - sehr niedrige Werte, die jedoch durch neuere Arbeiten grössenordnungsmässig recht gut bestätigt werden (11,12,13,14). Anschliessend wurden im Austausch mit Laboratorien in Europa und Uebersee Blutproben von belasteten und unbelasteten Personen untersucht, wobei sich signifikant höhere Werte als bei unseren beiden ersten Kollektiven ergaben. Beim Datenvergleich mit den anderen Laboratorien ergaben sich häufig gut übereinstimmende Mittelwerte, es wurden bisweilen aber auch erhebliche systematische Abweichungen beobachtet, deren Ursachen noch studiert werden müssen.

Tabelle VI zeigt einige dieser Ergebnisse. In allen Fällen zeigte sich der auch von anderen Autoren (11,13) beobachtete signifikant niedrigere Blutbleigehalt weiblicher Probanden. Derzeit kann noch nicht eindeutig geklärt werden, ob der Unterschied zwischen dem Mittelwert von Kollektiv A und dem von Kollektiv B zufällig oder relevant ist, da durchaus mit gerätebingten Schwankungen gerechnet werden muss. Aufgrund technischer Schwierigkeiten beim Probenaufschluss war es bisher nicht möglich, alle Vergleichsblutproben auch pulsepolarographisch zu überprüfen. Die bisher erhaltenen Werte - so vor allem beim Blut und auch bei Urin - bestätigen jedoch die Grössenordnung der routinemässig erhaltenen AAS-Werte.

In Tabelle VII sind Vergleichswerte zwischen AAS und Pulse-Polarographie zusammengestellt.

typ- oder gerätebedingt sind. Wir untersuchen derzeit dieses Phänomen unter Heranziehung weiterer AAS-Geräte.

Die Messungen von Pb in Haarproben konnten nach Aufschluss mit HNO_3 ohne Schwierigkeiten - Bestimmung durch standard addition - mit guter Reproduzierbarkeit durchgeführt werden. In Tabelle X sind die Werte zusammengefasst, die aus Haarproben von 30 nicht belasteten Personen aller Altersstufen stammen.

Auffallend ist die grosse Streubreite unabhängig vom Alter der Versuchspersonen, die wohl durch die geringe Einwaage - es wurde zu Testzwecken vorwiegend in der Mikroapparatur aufgeschlossen - mit bedingt sein dürfte.

Schliesslich enthält Tabelle XI einige Resultate von mit der flammenlosen AAS nach dem in Tabelle II angegebenen Zersetzungsprogramm durchgeführten Cd-Bestimmungen in stark verdünntem, hämolysiertem Blut. Die Werte sind verglichen mit der Literatur verhältnismässig hoch (15) und konnten bisher noch nicht durch Vergleichsmessungen mit der Polarographie gesichert werden. Auch kann eine Kontamination derzeit noch nicht ausgeschlossen werden.

Aufgrund unserer bisherigen Studien sehen wir zukünftig gute Möglichkeiten ebenso in einer Teilautomatisierung von Auschluss- und Bestimmungsmethoden wie in der Einführung weiterer Techniken, die Multieelementbestimmungen erlauben. Der Trend wird dabei sicher dahin gehen, aus Zeit- und Kostengründen mit den minimal möglichen Einwaagen auszukommen.

Durch gute zeitliche Nutzung aller Geräte und zuverlässiger Datenbanken in Kombination mit relevanten Modellen für den Spurenmetallfluss in Umweltkompartimenten sollte es möglich sein, die absolute Zahl der Analysen auf ein vernünftiges Mass zu begrenzen.

Wir danken dem Bundesministerium für Forschung und Technologie der BRD, Bonn, für die grosszügige Unterstützung, Perkin-Elmer, Deutschland, für die Ueberlassung des Prototypautomaten, den Kollegen Dr. Delves, London; Dr. Kubasik, Rochester, N.Y., USA; Dr. Kilroe-Smith, Johannesburg, Südafrika , sowie dem britischen Arbeitsministerium für Vergleichsblutproben.

LITERATURANGABEN

[1] KEPPLER, J.F.; MAXFIELD, M.E.; MOSS, W.D.; TIETGEN, G.; LICH, A.L.
Amer.Ind.Hyg.Assoc.J. 31, 417 (1970)

[2] BERLIN, A.; DEL CASTILHO, P.; SMEETS, J., Eur 5004 d-e-f, 1973,
p. 1033

[3] BERLIN, A.; LAUWERYS, R.; BUCHET, J.P.; ROELS, H.; DEL CASTILHO, P.;
SMEETS, J., Diese Konferenz, Beitrag 141

[4] STOEPPLER, M.; HILPERT, K.; VALENTA, P.; NUERNBERG, H.W.,
Z.Anal.Chem. im Druck

[5] NUERNBERG, H.W.; STOEPPLER, M.; VALENTA, P.,
Thalassia Jugoslavica, im Druck

[6] HAGEDORN-GOETZ, H.; STOEPPLER, M.,
Arch.Toxicol., im Druck

[7] BRANDT, K.; HAGEDORN-GOETZ, H.; STOEPPLER, M.,
Ber.d.KFA Jülich, im Druck

[8] STOEPPLER, M.; BACKHAUS, F.; KLAHRE P.
Z.Anal.Chem., in Vorbereitung

[9] PICKFORD, C.J.; ROSSI, G.,
Analyst, 97, 647 (1972)

[10] BARKER, G.C.; GARDNER, A.W.,
AERE-Report C/R 2297, Harwell 1958

[11] SCHMIDT, D.; SANSONI, B.; KRACKE, W.; DIETL, F.; BAUCHINGER, M.;
STICH, W.,
Münchener med. Wochenschr. 114, 1961 (1972)

[12] HAAS, Th.; WIEDE, A.G.; SCHALLER, K.H.,
Zbt.Bakt.Hyg.J.Abt.Orig.B. 155, 341 (1972)

[13] STUIK, E.J.; ZIELHUIS, P.L.,
Diese Konferenz, Beitrag 57

[14] HOWER, J.; PRINZ, B.; GONO, E.; REUSMANN, G.,
Diese Konferenz, Beitrag 61

[15] GELDMACHER, V.; MALLINCKRODT, M.; OPITZ, D.,
Arbeitsmedizin, Sozialmedizin, Arbeitshygiene, 10, 276, (1968)

2247

PANEL DISCUSSION

Preceding page blank

SUMMARY OF DISCUSSION

SZADKOWSKI (B.R.D.)

Das Thema der Sitzung sind Gewebsmessungen, und wer sich mit dieser Materie befasst hat weiss, dass hier erhebliche Schwierigkeiten auftreten können, etwa gegenüber Messungen in wässriger Lösung. Ursächlich dafür verantworlich zu machen sind die sehr zahlreichen anderen Substanzen, die in biologischen Materialien vorhanden sind und die unter Umständen stören können. Insbesondere möchte ich hier Eiweisskörper nennen. Wenn wir hier über Gewebsmessungen sprechen, dann meinen wir dabei auch Blut und Harn. Es wird allerdings auch gesprochen werden über Messungen in Leber, Knochen und auch in einigen Nahrungsmitteln. Für die im Rahmen dieser Sitzung interessierenden Schadstoffe, nämlich Schwermetalle, sind in den vergangenen Jahren eine ganze Reihe brauchbarer Methoden entwickelt worden.

Im Rahmen der weltweit mit Intensität angegangenen Probleme des Umweltschutzes sind nun internationale Vergleiche unumgänglich notwendig. Es ergaben sich hierbei jedoch neue Schwierigkeiten, die unter anderem in der unterschiedlichen Methodik, in der verschiedenen Probenahme und auch in der Aufbewahrung dieser Proben zu suchen sind. Es wird sich im Laufe dieser Sitzung zeigen, wie wichtig, aber auch wie schwierig durchzuführen derartige Vergleichsprogramme sind. Auf einem ganz anderen Sektor, nämlich auf dem der klinischen Labordaten, werden seit kurzem in der Bundesrepublik Deutschland Qualitätskontrollen von der zuständigen Bundesärztekammer verbindlich vorgeschrieben. Sie umfassen neben den regelmässig, d.h. bei jeder Analysen-Serie durchzuführenden Präzisionskontrollen auch Ueberprüfungen der Richtigkeit, d.h. der "accuracy". Die Vorschriften für die Durchführung dieser Qualitätskontrollen sind sehr detailliert

Preceding page blank

und präzise. Unrichtige Ergebnisse können für die betreffenden Laboratorien finanzielle Einbussen zur Folge haben. Ich möchte nun nicht hier dafür plädieren, derartige verbindliche Richtlinien auch für Messungen im Bereich der toxikologischen Umweltbelastung einzuführen. Es wäre international verbindlich gar nicht möglich, es würde ausserdem die Gefahr einer Stagnierung der entsprechenden Forschungssektoren bedeuten. Ich wollte aber demonstrieren, dass auch administrativ die Notwendigkeit vergleichbarer Resultate erkannt worden ist. Nun ist die Problematik vergleichbarer Resultate in der Analytik umweltrelevanter Stoffe ungleich differenzierter als im Bereich des Klinischen Labors.

Hierfür sind insbesondere die sehr viel niedrigeren Konzentrationen in den biologischen Materialien verantwortlich zu machen. Es ist daher nur zu begrüssen, wenn auf internationaler Ebene Vergleichsuntersuchungen gestartet werden und zwar nicht nur im Bereich der europäischen Gemeinschaft sondern auch über Atlantik und Pazifik hinweg. Ebenso bedeutsam ist das Bemühen um eine verfeinerte und verbesserte Methodik, die insbesondere abzielt auf die Verwendung immer kleinerer Probenmengen. Dies ist ein Punkt,der besonders wichtig ist für die breite Durchführung von epidemiologischen Untersuchungen.

The subject of this session is measurements in tissue, and anyone who has worked with this matter will know that considerable difficulties can arise, as compared for example with measurements in aqueous solution. Blame for this can be laid primarily on those numerous other substances present in biological materials which under certain circumstances can result in interference. I should particularly like to mention proteins among these. When we talk here of measurements in tissue we also include blood and urine. Furthermore, measurements in liver, bones and some foodstuffs are also included. In recent years a whole series of useful methods has been developed for the toxic substances which concern this session, i.e. heavy metals.

In connection with the world-wide problems of environmental protection which are being earnestly tackled, international comparisons are now unavoidably necessary. This gives rise to new difficulties, however, which include differing methodology, varied sampling and the preservation of the samples. During

the course of this session it became clear how important it is to carry out such comparison programmes, but also how much difficulty is involved. In a quite different field, namely that of clinical laboratory data, quality control by the competent Federal medical Association has recently been made compulsory in the Federal Republic of Germany. In addition to the regular precision controls carried out in every test series this also includes checks on accuracy. The test rules for these quality controls are very detailed and precise. Incorrect results may mean financial losses for the laboratories concerned. I am not suggesting we introduce compulsory rules of this kind for monitoring in environmental toxicology. These would not be enforceable on a world-wide scale and might in any case create a danger of stagnation in the sectors of research concerned. What I wanted to show was that administrative circles have also recognised the need for comparable results. But the question of comparable results from the analysis of environmental substances entails more widely differing nuances than clinical laboratory experiments. The far lower concentrations in the biological substances are particularly responsible for this. It is thus an excellent thing that comparative research has begun not only within the European Community but also across oceans and continents. Equally significant are efforts towards improved, more sophisticated methods using ever smaller samples. This point is especially important for the execution of wide epidemiological studies.

DISCUSSION

TATI (Japan)

In cadmium determination, Dr. Kjellström showed the systematic difference between Japanese and Karolinska studies, and also showed the different recovery rates between the two countries. What do you think about the correlation between the different values and the recovery rates of these two countries?

KJELLSTRÖM (Sweden)

Of course, this study has only shown that there is a difference and the deviation between duplicate samples in each laboratory is rather small so there must be some kind of systematic difference. Whether this means that the atomic absorption and neutron activation analyses done in Sweden have a lower recovery or that the atomic absorption analysis performed in some of the Japanese laboratories for some reason gives too high values we cannot exactly say. However, the Swedish atomic absorption method has been checked with the addition of radioactive cadmium to grains and we found that the recovery was 95%. There may be reasons to believe that at this rather low level of cadmium concentration in grains, there may be an exaggeration of the cadmium levels when using the Japanese methods. May I also say that there have been four different analytical laboratories participating from Japen, but unfortunately two of them only analysed five of the samples. The analyses from these two laboratories correlated very well with the neutron activation and the Swedish atomic absorption analysis.

MOORE (U.K.)

The 700°C Dr. Jeanmaire quoted for dry ashing of bone would appear to be too high. Work by our laboratories and by Hislop at Harwell indicated a loss of lead from bone at a temperature as high as this. We use a temperature no higher than 450°C and Hislop, 600°C. Could you comment on your temperature of 700°C?

JEANMAIRE (France)

Le problème de la température de minéralisation dépend certainement beaucoup des conditions opératoires et de la nature de l'échantillon. La question s'est déjà posée en radioactivité par exemple avec le cesium 137 et surtout le polonium 210 qu'on retrouve dans les os même après minéralisation à 700°, alors

qu'il est extrêmement volatil. La minéralisation est effectuée par paliers à 200°, puis à 400° et ensuite la température est amenée progressivement à 700°. Lorsque le poids de l'échantillon à minéraliser est faible, la température finale joue un rôle très important pour les pertes. Lorsque le poids de l'échantillon et celui du résidu sont grands, si l'élimination de la majorité de la matière organique est effectuée à une température assez basse pour éviter les pertes, je crois que l'on peut chauffer plus fortement ensuite, sans risque. C'est ainsi que nous avons porté jusqu'à 800° un phosphate de Ca contenant du plomb, sans mettre en évidence de perte appréciable en cet élément.

The question of mineralization temperature certainly depends to a large extent on operating conditions and the nature of the sample. The question has already arisen in radioactivity, for instance with caesium 137 and more particularly with polonium 210 which occurs in the bones even after mineralization at 700°C, then 400°C, the temperature thereafter being brought gradually up to 700°C. When the sample is light in weight, the final temperature has a very considerable bearing on the losses. When the sample and residue are heavy, and most of the organic matter is eliminated at a low enough temperature to avoid losses, I think there is no risk in stepping up the temperature afterwards. Thus we heated to 800°C a Ca phosphate containing lead without appreciable lead loss.

PFANNHAUSER (Austria)

Ich möchte die vorherige Diskussionsbemerkung unterstützen. Nach Untersuchungen in unserem Institut in Wien waren bei Trockenveraschungen über 450°C Verluste zu beobachten.

As a result of research undertaken in our Institute in Vienna, losses were observed in dry ashing at temperatures over 450°C. Perhaps Dr. Kjellström can tell us about his experience with dry ashing?

KJELLSTRÖM (Sweden)

The temperature of dry-ashing is 450°C and it is done in a special muffle oven, which is constructed to keep the temperature within ± 10°C. The sample is ashed during 15 hours. This procedure is done twice with the position of the crucibles reversed within the oven between the ashing procedures. We have studied the losses in each different step and found that the total loss is 5% and most of this is in the dry-ashing step. If we do wet-ashing and extraction in an organic solvent of grain samples we get a loss of 15% with most of this in the extraction procedure. After studying the losses in each step of the procedure we concluded that with this type of oven and at this temperature dry-ashing of wheat samples is possible to use for cadmium analysis.

CERNIK (U.K.)

Has Dr. Berlin considered the use of EDTA for the homogeneous preservation of lead in blood, to prevent the variability of results due to non-representative sampling? The use of heparin can be a disadvantage with postal delayed samples because of viscosity changes and possible clotting.

BERLIN (C.E.C)

In the first instance we allowed each of the laboratories to use the techniques of their choice and most of them preferred heparin for preservation. We were aware of your work and in view of the rather unsatisfactory results which were obtained, I feel we should examine again the possibilities of using EDTA. We had some problems with the containers for cadmium in urine and for the aqueous mercury solutions. We are considering using in future programmes quartz which should certainly reduce absorption and contamination problems.

Truffert (France)

J'ai constaté des pertes de plomb lorsque l'incinération se faisait à une température supérieure à 500°C, même sur les os. Cependant, pour ces derniers, la perte était moins importante que pour des denrées alimentaires beaucoup moins riches en calcium, qui paraît retenir le plomb. La volatilisation des toxiques minéraux dépend beaucoup de la nature du milieu traité. C'est ainsi qu'en ajoutant de l'acide nitrique aux cendres, on peut accélérer la minéralisation sans perte de plomb. Mais alors les pertes de cadmium sont considérables, ce qui n'est plus le cas si l'on ajoute de l'acide sulfurique, les sulfates de ces métaux n'étant guère volatiles.

Personnellement, j'effectue des minéralisations à basse température (au voisinage de 360°C) dans un incinérateur sous courant d'oxygène filtré , mis au point avec Mme Girard-Walton.

I have observed lead losses when the incineration temperature was over 500°C, even in bones. Even so, the loss was not so great as for foodstuffs more deficient in calcium which appears to retain lead. The volatilization of toxic minerals depends to a large extent on the type of medium treated. Thus, if nitric acid is added to ash, mineralization can be accelerated without lead loss. Cadmium losses are then considerable, however, but this is not the case if sulphuric acid is added, since sulphates of these metals are not very volatile.

Personally, I conduct low-temperature mineralizations (about 360°C) in an incinerator with a stream of filtered oxygen, developed with Mrs. Girard-Walton's help.

BRAETTER (B.R.D.)

Dir Frage richtet sich an Dr. Jeanmaire. Haben Sie bei Ihren Untersuchungen den vollständigen Wirbel bzw. die Rippe zur Analyse eingesetzt oder nur Teilproben? Bei systematischer Durchmusterung von menschlichen Skeletten haben wir die ortliche Verteilung von 20 - 30 Spurenelementen mit Hilfe der Neutronenaktivierungsanalyse untersucht. Es zeigte sich, dass innerhalb

enger Bereiche bei verschiedenen Spurenelementen Konzentrationsänderungen bis zu zwei Zehnerpotenzen auftreten, die mit Besonderheiten der Knochenphysiologie im Zusammenhang stehen. Deshalb sollte bei Knochenanalysen dem Ort der Probenahme sehr grosse Aufmerksamkeit geschenkt werden.

I would like to ask Dr. Jeanmaire if he used the entire vertebra or rib for the analysis or only sections of them? In a systematic examination of human skeletons we determined the local distribution of 20 to 30 trace elements using neutron activation analysis. This showed that within very limited areas, concentration variations of up to two decades occur for several trace elements. These are related to certain features of the osteophysiology. Great attention should be paid, therefore, to the location of the bone sample taken.

JEANMAIRE (France)

Les côtes sont en général des côtes flottantes; nous avons la totalité de l'os qui est minéralisé puis broyé pour obtenir un échantillon moyen. Les vertèbres sont entières également.

The ribs are usually floating ribs; the entire bone is mineralized and crushed to obtain an average specimen. The vertebrae are also entire.

SZADKOWSKI (B.R.D.)

Ein wesentliches Anliegen dieser Sitzung war ein Erfahrungsbericht zu geben über die Durchführung internationaler Vergleichsprogramme. Wir haben gehört und auf den Diapositiven auch gesehen, dass die Ergebnisse eigentlich noch lange nicht so sind wie wir sie uns wünschen. Es stellt sich die Frage ob derartige Vergleichsprogramme überhaupt nützlich sind und wenn ja wie sie durchgeführt werden können, wie sie verbessert werden können?

A fundamental concern of this session was to present a report on the experiences made in the implementation of intercomparison programmes. We have seen, that the results are far from what we desired to have. The question now arises if such comparison programmes serve any useful purpose and if so, in what ways can they be improved?

KJELLSTRÖM (Sweden)

I think it is very important when you do intercomparison studies to take sufficient numbers of samples so that you can make conclusions regarding systematic differences between the laboratories. If you ship urine and blood all over the world there may be, especially for low concentration samples, wall effects etc., which make the actual concentration in the subsample received by certain laboratories different from the average. So I think that at least 10 samples of blood or 10 of urine should be exchanged in such a study. It is also important that participating laboratories are identified and that the methods used are described in reasonable detail.

BERLIN (C.E.C.)

The second intercomparison programme on lead having shown no real improvement over the first, one point must be emphasised: we had more than doubled the number of participating laboratories and furthermore, some of the laboratories that took part in the first did not take part in the second. We still strongly feel that intercomparison programmes serve to improve the results, and this is fundamental. Following an intercomparison programme we often organize a meeting of the participating laboratories so that they may discuss the results in depth. This does lead to one difficulty, the need to lift the anonymity of the laboratories during the meeting in order that full discussions may be held.

A further point regarding the quality assurance; since for environmental measurements the concentrations are very low and thus the analyses difficult, national and international authorities when they contract for research in this field should assure themselves of the quality of the analyses which will be performed by the laboratories. One should really have results at hand of which one can be sure that they are objective and not questionable, at least from the analytical point of view. One will always be able to discuss other aspects of the results but the long discussions on the validity of the analyses should be curtailed.

DELVES (U.K.)

I would agree with Dr. Berlin about removing any 'anonymity' from the discussions after the results have been disclosed and I think this should be agreed before the analyses are carried out. But one of the big difficulties in carrying out interlaboratory comparative analyses is that one ends up with a whole series of results and there still remains the question which is the right answer? A procedure that might overcome this problem would be for the reference laboratory to use at least three different analytical techniques to carry out the analysis of the stock sample. These techniques should be based on different physical or chemical concepts, for example, anodic stripping voltammetry, colorimetry, atomic absorption, and then as the National Bureau of Standards in Washington does, the reference laboratory could issue a certified value together with a range of acceptable values. If any laboratory did not report analyses within this range, that laboratory would be in error and one could at least start to discuss the reasons for this.

Secondly, I would like to see at least on spiked sample used for the intercomparison study. I am aware that the metal added will not be in the same form as that originally present in the sample, but one would know exactly the difference in concentrations between the spiked and unspiked sample and those laboratories that did not obtain this difference would be in error.

In my opinion the use of spiked samples together with samples that have been given a range of 'acceptable concentration' by the reference laboratory would help to solve some of the problems of interlaboratory comparative analyses.

STÖPPLER (B.R.D.)

Ich möchte mich den Vorträgen der beiden Vorredner anschliessen und meine, dass wir im Augenblick einen Stand erreicht haben, bei dem es eigentlich nicht so sehr darauf ankommt, dass eine sehr grosse Zahl von Laboratorien an Tests dieser Art teilnehmen, sondern dass in einem verhältnismässig kleinen, aber sehr qualifizierten Kreis diese Dinge noch etwas intensiver studiert werden sollten.

In my opinion we have now reached a stage at which it is not necessary any more that a very large number of laboratories take part in these tests, but rather that a relatively small number of highly qualified experts should make a more intensive study of these problems.

SZADKOWSKI (B.R.D.)

Ich darf vielleicht noch folgende Anregung geben. Auch bei wissenschaftlichen Veröffentlichungen, die sich nicht direkt mit methodischen Problemen befassen, sollte doch die Methode angegeben werden, und es sollte zumindest darauf hingewiesen werden, wo man über die Zuverlässigkeit dieser Methode nachlesen kann, damit bei einer kritischen Auswertung der Literatur wie wir sie kürzlich in Zusammenarbeit mit europäischen Gemeinschaften versucht haben, den einzelnen Autoren eine bessere Uebersicht möglich ist. Im übringen danke ich für die sehr rege Diskussion.

In closing a suggestion should be made. Even in scientific publications which do not deal directly with methodological problems the methods should nevertheless be described and at least an indication should be given of the relevant literature on the reliability of these methods. This would give a much clearer picture to those who have to evaluate critically this literature, as we have done recently in cooperation with the European Communities.

2261

GEWEBSMESSUNGEN
TISSUE MEASUREMENTS
MESURES RELATIVES AUX TISSUS BIOLOGIQUES
MISURE NEI TESSUTI BIOLOGICI
METINGEN VAN BIOLOGISCH WEEFSEL

(Continued)

Panel

Vorsitzender - Chairman - Président - Presidente - Voorzitter

O.A. WEBER (Jugoslavija)

Preceding page blank

THE CONCENTRATIONS OF COPPER, IRON, MANGANESE, ZINC AND CADMIUM IN HUMAN HAIR AS A POSSIBLE INDICATOR OF THEIR TISSUE CONCENTRATIONS

E. VUORI, A. HUUNAN-SEPPÄLÄ AND J. O. KILPIÖ

Department of Public Health Science, University of Helskini,
Finland

ABSTRACT

Samples from lung, muscle, liver, kidney and hair were collected from 20 accidentally dead persons. The tissue concentrations of copper, iron, manganese, zinc and cadmium were determined by atomic absorption spectrophotometry using both flame- and flameless atomizing systems. Linear coefficient of correlation was calculated between different tissues for each element measured.

The amounts of the trace elements measured in tissues in the present study were approximately the same order as those reported in literature for Finnish population. However, in our material the values of copper in tissues were about two times higher than those reported earlier.

In the present study no significant correlation between the contents of trace elements in hair and other tissues was found. Almost significant correlations were found between the cadmium contents of hair and lung and between the zinc contents of hair and muscle. It seems to us that the concentrations of trace elements in human hair hardly can be used as an indicator of their concentrations in other tissues as far as the trace elements included in this study are concerned and the concentrations of these trace elements fall into a "normal" range.

Preceding page blank

Introduction

There has been a great number of studies in litterature concerning the amount of various trace elements in human tissues. The tissue concentrations of trace elements are considered to be of great importance since measuring only e.g. air, water or food does not give reliable information about the status of trace elements in human body and about their acute and chronic effects on tissue metabolism. The specimen collection for the determination of trace element is rather easy as far as autopsy material is concerned. The opposite is true of healthy human beings whose tissue concentrations have been difficult to study mainly due to the problems of getting biopsy material. It is concidered that serum as a study material has many important disadvantages (Strain et al. (11), Hammer et al. (6), Hambidge (5)). Therefore it seems to be quite natural that scalp hair has been considered as a "promising" subject for trace element determinations for years. Taking a hair biopsy is readily atraumatically performed and it is easy to collect even large quantities of this material.

On one hand it has been supposed that the concentrations of some trace elements in human hair can be used as an indicator of the contents of these elements in tissues (Goldblum et al. (2), McDonald and Warren (8), Strain et al. (11)), on the other hand it has been warned that the contents of trace elements in hair are not very indicative of their tissue concentrations and interpretation of analytical data requires caution (Schroeder and Nason (10), Hambidge (5)). Therefore a controlled study about this problem seemed to us necessary to perform as a part of the trace element project carried out in our laboratory.

This preliminary report reveals some of our main findings concerning the trace element contents of hair and other tissues. The whole material will be published later in detail.

Materials and methods

Samples from lung, muscle, liver, kidney and hair were collected from 20 accidentally died persons. For analysis the soft tissue samples were dried overnight at 100°C and then muffle-furnace ashed at 450°C in quartz crucibles. Hair samples were washed before ashing as follows: the samples were first pre-washed several times with deionized water and then once with ethanol. After the pre-washing the hair samples were washed in a shaker first once with n-hexane and then four times with 1 % sodium laurylsulphate. Each washing in the shaker lasted 20 min. After all these successive washings the hair samples were finally very thoroughly washed with deionized water and then dried overnight at 100°C. Detailed description about the hair washing procedure and about its effects on the trace element concentrations of hair will be published. In this connection it can be said that the washing procedure had actually no effect on copper, zinc and cadmium levels of hair but the opposite was true on iron and manganese levels.

For hair analysis we used only a certain part of the whole sample, that is 1-2 cm measured from the scalp. The ashing procedure of the hair samples was similar to the tissue ashing. The ash was dissolved in 2 ml of 4 M HCl and diluted to 10 ml using deionized water. The trace metal conccentrations of this solution were determined by atomic absorptions spectrophotometry using both flame- and flameless atomizing system (Perkin Elmer 300, HGA 70).

In all different phases of the analytical procedure care was taken to avoid all possible sources of contamination. All reagents and washing agents were checked not to cause contamination and all glass-ware used was carefully washed and dried before use.

About the statistical analyses a detailed description will also be published later.

Results

The concentrations of copper, iron, manganese, zinc and cadmium were determinated in hair, muscle, lung, liver and kidney. Linear coefficient of correlation was calculated between different tissues for each element measured.

Table I The trace element concentrations of tissues investigated

	Hair	Muscle	Lung	Liver	Kidney
Cu	23.3	6.07	6.87	23.6	13.9
	18.5	3.2	2.4	10.9	4.5
	(6.25)[6]	(<2.8)[19]	(3.4)[19]	(18.3)	(7.9)[19]
Fe	77.3	128	1148	549	398
	84	25	464	217	193
Mn	1.56	0.84[19]	1.35	5.11	4.99
	1.23	1.36	1.08	1.46	0.79
	(1.36)[3]	(<0.4)[18]	(<0,6)[11]	(3.8)[12]	(2.26)[10]
Zn	199	230	67.2	197	194
	64	52	17.5	66	38
	(107)[6]	(232)[19]	(53.0)[19]	(298)	(173)[19]
Cd	0.35	0.20[16]	1.86[16]	4.15	73.2
	0.27	0.13	1.30	3.68	38.2
	(<0.27)[6]	(<1.6)[19]	(1.14)[19]	(3.8)	(40.7)[19]

The numbers denote µg/g in dry weight. The first number in each group denotes mean, the second sd and the number in brackets denotes value which has been reported earlier for Finnish population. If not otherwise informed the number of cases is 20.

Table II The correlations of trace elements measured between the tissues in question

Cd	muscle	lung	liver	kidney
hair	ns	+	ns	ns
muscle		ns	+	++
lung			ns	+
liver				+

Cu	muscle	lung	liver	kidney
hair	ns	ns	ns	ns
muscle		ns	ns	++
lung			++	++
liver				+

Fe	muscle	lung	liver	kidney
hair	ns	ns	ns	ns
muscle		ns	$\underline{+}$	ns
lung			ns	++
liver				ns

Mn	muscle	lung	liver	kidney
hair	ns	ns	ns	ns
muscle		ns	ns	ns
lung			ns	ns
liver				ns

Zn	muscle	lung	liver	kidney
hair	+	ns	ns	ns
muscle		ns	ns	ns
lung			+	ns
liver				ns

ns denotes not significant ($p > 0.05$)
+ denotes almost significant ($0.05 > p > 0.01$)
++ denotes significant ($0.01 > p > 0.001$)
$\underline{\quad}$ denotes negatively correlated

Table I shows the trace element concentrations of tissues investigated and Table II shows the correlations of trace elements measured between the tissues in question. As a whole it can be seen in these tables that the concentrations of trace elements investigated do not generally correlate with the amounts of these elements in other tissues used in this study. However, cadmium correlates significally between muscle and kidney and almost significally between hair and lung, muscle and liver, lung and kidney, liver and kidney. Copper correlates significally between muscle and kidney, lung and liver, lung and kidney and almost significally between liver and kidney. Iron correlates significally between lung and kidney and almost significally but negatively between muscle and liver. Manganese shows no correlation between tissues investigated. Zinc correlates almost significally between hair and muscle, lung and liver.

Discussion

It has been shown that sex, age and hair colour have influence on hair trace element concentrations (Schroeder and Nason (10), Petering et al. (9)).Furthermore Hambidge (5) has shown that copper concentrations even depend on sampling **technique** so that the distal parts of hair contain more copper than the proximal parts. Our material consisted of 20 accidentally died persons of whom 14 were men and 6 women (mean age 34.5 years, range 13-78 years). All of them had natural hair colour. Only the very proximal part of hair was used in the present study. Muscle samples had been taken from m. pectoralis major, liver and lung samples represented parenchyma and kidney samples both cortex and medulla.

Hambidge (4) has pointed out that the hair analysis of chromium as an indicator of the nutritional status is valuable if the correlation between chromium in hair and other organs is determinated. There is no reason to suppose that this concept is not valid as far as other trace elements are concerned, too. However, studies where human hair trace element concentrations have been correlated with those of other tissues are quite few (Goldblum et al. (2), McDonald and Warren (8)).

The amounts of the trace elements measured in tissues in the present study were approximately the same order as those reported in litterature for Finnish population. The only exception was copper: in our material the values of copper in tissues were about two times higher than those reported earlier by Forssén (1).

In the present study no significant correlation between the contents of trace elements in hair and other tissues was found. Almost significant correlations were found between the cadmium contents of hair and lung and between the zinc contents of hair and muscle. On the basis of these results the earlier suspicions of the value of hair as a biopsy material in this respect have received more attention. This is solid as far as the trace elements included in this study are concerned and the concentrations of these trace elements fall into a "normal" range. The opposite might be true when specimens are taken from persons suffering from a disease that is known to cause disturbance in trace element metabolim (Hambidge et al. (3), McDonald and Warren (8)). The situation might be the same for the nonessential trace elements (e.g. arsenium, cadmium, lead, mercury). In these cases human hair has been used to indicate the degree of exposition to these elements (Hammer et al. (6), Kopito et al. (7)). The biopsies used in this study were taken from subject representing "normal" population with no apparent exposition.

References

1 FORSSÉN, A., "Occurance of Ba, Br, Ca, Cd, Cs Cu, K, Mn, Ni, Sn, Sr, Y and Zn in the human body", *Ann.Med.Exp.Bio. Fenniae*, 50, 99 (1972)

2 GOLDBLUM, R.W., DERBY, S., LERNER, A.B., "The metal content of skin, nails and hair", *J.Invest.Dermatol.*, 20, 13 (1953)

3 HAMBIDGE, K.M., RODGERSON, D.O., O'BRIEN, D., "Concentration of chromium in the hair of normal children and children with juvenile diabetes mellitus", *Diabetes*, 17, 517 (1968)

4 HAMBIDGE, K.M., BAUN, J.D., "Hair chromium concentrations of human newborn and changes during infancy", *Am.J.Clin. Nutr.*, 25, 376 (1972)

5 HAMBIDGE, K.M., "Increase in hair copper concentration with increasing distance from the scalp", *Am.J.Clin.Nutr.*, 26, 1212 (1973)

6 HAMMER, D.I., FINKLEA, J.F., HENDRICKS, R.H., SHY, C.M., HORTON, R.J.M., "Hair trace metal levels and environmental exposure", *Am.J.Epiodemiol.*, 93, 84 (1971)

7 KOPITO, L., BRILEY, A.M., SCHWACHMAN, H., "Chronic plumbism in children: Diagnoses by hair analysis", *JAMA*, 209, 243 (1969)

8 MACDONALD, I., WARREN, P.J., "The copper content of the liver and hair of African children with kwashiorkor", *Brit. J.Nutr.*, 15, 593 (1966)

9 PETERING, H.G., YEAGER, D.W., WITHERUP, S.O., "Trace metal content of hair 1. zinc and copper content of human hair in relation to age and sex", *Arch.Environ.Health.*, 23, 202 (1971)

10 SCHROEDER, H.A., NASON, A.P., "Trace metals in human hair", *J.Invest.Dermatol.*, 53, 71 (1969)

11 STRAIN, W.H., STEADMAN, L.T., LANKAU, C.A. JR., BERLINER, W.P., PORIES, W.J., "Analysis of zinc levels in hair for the diagnosis of zinc defiency in man", *J.Lab.Clin.Med.*, 68, 244 (1966)

TRACE ELEMENTS IN LUNG AND HAIR

G. W. GIBBS AND E. BOGDANOVIC

Department of Epidemiology and Health, McGill University, Montreal, Canada

ABSTRACT

In order to determine the health effects of airborne inorganic particulates on man, it is first necessary to establish reliable methods of measuring exposure. Lung burden might be a useful index, but there is little information on it's relationship to measured concentrations of airborne particulates and rates of removal of air pollutants from the lung. Studies to clarify these relationships and associations between the concentrations of trace elements in lungs and disease in man are often hampered by the difficulty of obtaining whole lungs for analysis. An alternative method is to use a portion of lung, but this requires knowledge of the way in which particulates are distributed within the lung.

Sixteen right lungs and four left lungs have been analysed by bronchopulmonary segments for fourteen metals. Preliminary observations based on these results indicate that elements are not uniformly distributed in the lung, the concentrations of most elements analyzed (μg/g lung ash) being highest in the apex and lowest in the anterior segments. The total quantity of several elements, in particular nickel and cobalt, increased with age. These and other elements present in the lung were related to one another, copper being highly correlated with the calcium content.

Assuming the trace element content of the lung to be a reasonable index of exposure to airborne inorganic particulates, preliminary results suggest that the concentrations of trace elements in hair are unlikely to provide a useful index of exposure to inorganic atmospheric pollutants by the general population.

1. Introduction

The mineral constituents of lung and other human tissues can be divided into two groups depending on their concentration (Koch et al [1]). First the elements such as calcium, sodium and potassium, which are generally present in high concentrations (mg/100 g wet tissue). Elements may be "essential elements" involved in metabolism or contaminants which, depending on their chemical form and concentration, may or may not have an adverse effect on the organism.

The concentrations of the major elements and trace elements in lung and other tissues have assumed importance for a number of reasons. Large scale studies of metals have been undertaken to describe the distribution and concentration of stable elements in the organs and tissues of "standard man" upon which the International Commission on Radiological Protection [2] based MPC calculations. The mineral and trace element contents of the lungs of occupational groups such as coal workers have been studied for their relationship or roles in pneumoconiosis (Rossiter et al [3], Keenan et al [4]). The ability of certain metals to act as carcinogens in their own right or to play a role in carcinogenicity by inhibition of enzyme activity (Dixon et al [5]) has led to their study in cancerous and non-cancerous tissue (Mulay et al [6]).

In occupational studies it is often possible to make some assessment of particulate and even trace element exposure from environmental measurements (Gibbs and LaChance [7], Gibbs [8]), while for the general population measurements are rarely adequate. In order to determine the health effects of airborne inorganic particulates on man, it is first necessary to establish reliable methods of measuring exposure. Total lung burden may be a useful index but there is little information on its relationship to measured concentrations of airborne particulates and rates of removal of air pollutants from lungs. Studies to clarify these relationships and associations between the concentrations of trace elements in lung and diseases in man are often hampered by the difficulty of obtaining whole lungs for analysis and analysis of portions of lung require a knowledge of the distribution of trace metals and particulates within the lung.

Although it has been recognized for may years that elements such as arsenic are concentrated in hair, only recently with improved analytical methods have metals such as zinc, cadmium, copper, lead and mercury been detected. The presence of trace elements such as lead in hair opened new avenues of investigation as to the possible use of such a readily available tissue in a living population to measure the exposure of persons occupationally exposed to metals (El-Dakhakhny and El-Sadik [9]). As the exposure to metals by the general population is much lower and as there are sources of metal other than airborne particulates it is not known whether the trace metal content of hair from a non-occupational group reflects exposure to trace metals present in general air pollution.

This report describes preliminary results of a study of the distribution of trace elements in segments of lung and their relationship to a limited number of trace elements in hair.

2. Methods

2.1 Collection of Samples

Whole lungs and in most cases, scalp and pubic hair were collected at routine autopsies at seven centres in Montreal and neighbouring areas. Tissues were transferred directly to polyethylene bags provided for that purpose and were stored in a deep freeze until analysed. Hair samples, cut as close to the skin as possible, were placed in envelopes provided by the laboratory. For each case, age, cause of death and place of residence were ascertained. No attempt was made to select cases with specific causes of death (e.g. accidents), or to exclude cases unless the specimen was incomplete.

2.2 Sample Preparation

The lung was weighed and cut into the following bronchopulmonary segments

Left Lung		Right Lung			
Upper lobe	Apical	Upper lobe	Apical	Middle lobe	Lateral
	Anterior		Anterior		Medial
	Posterior		Posterior		
	Lingular				
Lower lobe	Superior Basal	Lower lobe	Superior Basal		
	Anterior Basal		Medial Basal		
	Lateral Basal		Lateral Basal		
	Posterior Basal				

Segments were weighed and dried in an oven at 110°C to constant weight. This took from one to four days. The specimens were then placed in a furnace for ashing. The furnace temperature was raised slowly (17 hours to reach 475°C) which prevented conflagrations which would cause serious sample losses. The tissue was ashed for four days, at the end of which period the ash weight was constant.

The ash from two lungs were analysed semi-quantitatively using X-ray fluorescence techniques to identify elements which were present in sufficient quantities for detailed analysis by atomic absorption spectrophotometry. For this prupose the ash was treated with a mixture of 1:1 concentrated nitric and perchloric acids and made up to volume in nitric acid.

Hair samples were washed and ashed using the method reported by Petering et al [10].

3. Results

3.1 Loss in Weight on Drying

The loss in weight of lungs dried in segments ranged 75.5 - 92.9% (mean 83.6%, median 83.3%) and of lungs dried in lobes ranged 65.2 - 86.9% (mean 80.0%, median 81.7%). This loss in weight was slightly higher than the published value of 78% (Diem [11]). The difference between the loss on drying of lungs in segments and lungs dried as complete lobes possibly reflected the difficulty of removing water from large fragments of unmacerated tissue. The loss in weight of individual segments was not analysed in detail but appeared to be reasonably uniform with a few exceptions where large differences in loss between lobes or segments were detected.

3.2 Lung Ash

The ash from most lungs was white but in some cases ash from different regions of the lung showed marked differences in colour. Ash as a percentage of wet and dry lung tissue weight is shown in Table I. Although some lungs showed considerable variation in the percentage of ash from individual segments, the overall ash weight was approximately one percent of wet tissue weight and six percent of dry tissue weight. The ash contents of the upper, middle and lower lobes of 12 right lungs and of the upper and lower lobes of six left lungs are shown in Table II. When the ash contents were expressed as mg/g wet or dry tissue weights, the results were similar for the three lobes, although there was a tendency for the

Table I

Ash content of lungs analysed by segment

	Lung No	Ash % Wet Weight Range	Ash % Wet Weight M	Ash % Dry Weight Range	Ash % Dry Weight M
Right Lungs (16)	85	0.8-0.9	0.8	6.8-8.3	7.5
	49	0.4-1.0	1.0	2.0-5.0	4.8
	73	0.4-1.3	0.4	5.2-17.7	6.8
	39	1.0-1.1	1.0	5.3-5.9	5.7
	77	0.8-0.9	0.8	5.6-6.9	6.1
	12	1.0-1.2	1.1	5.7-6.5	6.0
	78	0.9-1.0	1.0	4.5-8.4	5.9
	99	0.6-1.0	0.9	4.5-6.8	6.2
	100	0.8-1.1	1.0	5.1-6.3	5.6
	13	0.9-1.1	1.0	6.8-7.8	7.0
	23	0.8-1.0	0.9	4.7-5.6	5.2
	21	1.0-1.2	1.1	5.6-6.8	6.2
	17	1.2-1.4	1.2	5.2-5.7	5.3
	27	0.9-1.0	1.0	5.7-6.4	6.3
	33	0.9-1.0	0.9	5.0-6.0	5.6
	19	1.0-1.3	1.1	6.1-8.2	7.5
	Overall	0.4-1.4	1.0	2.0-17.7	6.1
Left Lungs (4)	4	0.9-1.3	1.0	5.6-7.6	6.6
	11	0.8-1.1	1.0	5.0-7.0	5.9
	64	1.0-1.1	1.1	6.0-6.6	6.3
	22	0.9-0.9	0.9	5.9-7.6	7.1
	Overall	0.8-1.3	1.0	5.0-7.6	6.0

Table II

Ash content of lungs analysed by lobe

	Lung No	mg Ash/g Wet Weight Upper Lobe	mg Ash/g Wet Weight Middle Lobe	mg Ash/g Wet Weight Lower Lobe	mg Ash/g Dry Weight Upper Lobe	mg Ash/g Dry Weight Middle Lobe	mg Ash/g Dry Weight Lower Lobe
Right	70	12	9	9	71	40	64
	71	10	10	-	54	54	57
	3	9	8	8	56	50	54
	47	10	10	10	57	52	56
	106	11	11	10	48	43	44
	108	13	12	10	72	64	59
	109	10	10	10	70	69	71
	110	11	11	11	56	56	57
	113	8	10	7	23	56	19
	117	10	10	7	50	76	40
	114	12	12	9	67	66	41
	101	12	11	11	54	52	47
	Overall	10	10	10	56	55	56
Left	115	6	-	9	117	-	100
	43	9	-	9	52	-	50
	107	10	-	9	99	-	56
	112	11	-	11	68	-	71
	83	11	-	9	69	-	63
	116	10	-	7	58	-	40
	Overall	10	-	9	69	-	59

ash content (mg/g dry wt.) to be higher in the left upper lobes than in the left lower.

3.3 Ash Content and Age

The ash content of lung in mg/g dry lung weight showed little relation to age and the linear correlation was low and negative (-0.25). However, the total ash weight increased with age (r=0.61). This suggests that both tissue weight and mineral within the lung increased with age, but tissue weight increased more rapidly.

3.4. Metals in Lung

The range and median concentrations of metals in lungs examined in this study are shown in Table III. With the exception of zinc, which occurred in lower concentration and calcium which was present in much higher concentration, the results were in good agreement with those of Tipton and Shafer (12) for victims of instantaneous death from nine cities in the USA. The higher calcium levels in our study may be related to the older population (Mean age 65.1 years).

3.5 Change in Metal Content of Lung with Age

If certain metals present in inorganic particulates are inhaled by the general population and retained in the lungs, the total quantity and concentration of those metals might be expected to increase with age. Certain endogenous metals might also increase with age. The relation of 10 metals to age and to other metals in twenty lungs (16 right and 4 left) are shown by the linear correlation matrix in Table IV. Nickel and cobalt were the elements most highly correlated with age (r=0.60 and r=0.50 respectively). Zinc showed no relationship to age. Of interest were the relatively low correlation of calcium with age (0.33) and the extremely high correlation of copper with calcium (0.93). Three elements showing little relation to calcium or copper were cadmium, aluminium and chromium.

3.6 Distribution of Metals within Lung

The concentrations of eleven metals (μg metal/g ash) in ten segments of sixteen right lungs and eight segments of four left lungs are shown in Table V. For the right lungs the ranges and median concentrations of the metals Ni, Co, Pb, Cr, Mg, Ca and Cu were lower in the second segment (Anterior). In left lungs, the concentrations of Ni, Co, Pb, and Mn were lower in segments two and four and the higher concentrations of Ni, Co, Pb, Mn, Cr and Zn were present in the first segment (Apex). Magnesium and aluminium appeared to be concentrated in the fifth segments. As the data presented here are preliminary they have not been subjected to rigorous statistical analysis. Nevertheless, it is apparent that certain metals are not uniformly distributed within the lung when expressed as concentrations per unit ash. It seems likely that metals entering the lung as air pollutants are concentrated in the apices of the lung but also enter other areas, but this interpretation is complicated by the interrelationships of the metals.

3.7 Trace Elements in Hair

The concentrations of Pb, Ni, Cu, Zn and Cd in scalp hair, pubic hair and lung are shown in Table VI. On these limited data there appeared to be little or no relationship between these metals in lung and concentrations of these metals in hair and no consistant relationship between the levels in scalp hair and pubic hair. Nickel was detected only in two specimens and then in high concentration. Zinc was present in all specimens in concentrations in the range reported by Petering et al [10] but to date too few specimens have been analysed to reliably examine relationships with age. However the scatter of the results makes it unlikely that hair samples will prove useful in studies to determine exposure to air pollutants.

Table III

Ranges and median concentrations of metals in lung (µg/g tissue ash)

LEFT LUNG.	Current series		Published data(10)	
Metal	µg/g Tissue Ash		µg/g Tissue Ash	
	range	median	range	median
Aluminium	304-7945	1925	170->4000	2000
Cadmium	10-214	54	<50-270	<50
Calcium	6591-91805	26522	400-29000	10000
Cobalt	5-50	20	<2-140	<2
Chromium	5-198	28	0.5-120	13
Copper	32-243	95	50-250	120
Iron	5009-150995	18080	-	-
Magnesium	2689-91805	8482	3800-16000	8600
Manganese	14-284	133	<10-170	10
Nickel	6-86	30	<5-800	<5
Lead	8-204	36	5-550	47
Potassium	8185-215025	33997	-	-
Zinc	16-1584	167	660-3100	1300
Sodium	94122-561694	211452	-	-

RIGHT LUNG.	Current series	
	g/g Tissue Ash	
Metal	range	median
Aluminium	80-7946	1080
Cadmium	3-639	55
Calcium	4037-215,300	29945
Cobalt	5-103	21
Chromium	8-843	47
Copper	38-347	107
Magnesium	1056-107,200	8813
Manganese	10-468	116
Nickel	6-126	27
Lead	5-416	50
Zinc	36-20,806	855

Table IV

Correlation matrix - age and the median lung content of 10 metals

	Age	Ca	Al	Zn	Ni	Co	Cr	Mn	Pb	Cd	Cu
Age	1.000	0.331	0.302	-0.004	0.602	0.500	0.409	0.308	0.284	0.114	0.388
Ca	0.331	1.000	-0.045	0.452	0.538	0.367	0.095	0.655	0.322	-0.178	0.928
Al	0.302	-0.045	1.000	-0.094	0.294	0.227	0.207	0.374	0.151	0.231	0.016
Zn	-0.004	0.452	-0.094	1.000	0.044	0.030	-0.160	0.205	-0.037	-0.111	0.452
Ni	0.602	0.538	0.294	0.044	1.000	0.369	0.477	0.565	0.293	-0.134	0.597
Co	0.500	0.367	0.227	0.030	0.369	1.000	0.693	0.654	0.569	0.247	0.416
Cr	0.409	0.095	0.207	-0.160	0.477	0.693	1.000	0.398	0.643	0.134	0.144
Mn	0.308	0.655	0.374	0.205	0.565	0.654	0.398	1.000	0.543	0.251	0.630
Pb	0.284	0.322	0.151	-0.037	0.293	0.569	0.643	0.543	1.000	0.315	0.264
Cd	0.114	-0.178	0.231	-0.111	-.0134	0.247	0.134	0.251	0.315	1.000	0.024
Cu	0.388	0.928	0.016	0.452	0.597	0.416	0.144	0.630	0.264	0.024	1.000

Table V

Range and median concentrations of metals in lung segments (μg/g ash)

Lung Segment	Ni		Co		Pb		Mn		Cr		Cd		Al	
	Range	M	Range	M	Range	M	Range	M	Range	M	Range	M	Range	M
(Right)														
1	9-126	43	10-103	40	34-275	99	64-329	145	24-258	84	8-327	53	250-7946	2001
2	6-29	18	5-21	9	7-70	32	10-196	115	8-78	21	3-235	32	192-4650	1438
3	8-63	31	6-67	15	25-416	48	27-317	126	10-843	33	5-383	24	197-4833	1316
4	8-88	27	7-68	21	11-181	61	14-280	117	10-170	41	5-639	65	139-4205	1102
5	11-59	29	13-58	21	5-234	43	23-468	124	19-146	53	6-482	56	170-2463	714
6	8-57	21	10-38	17	20-150	52	14-364	81	19-94	48	9-327	72	135-2687	858
7	10-67	27	8-52	24	18-244	67	45-279	122	16-132	66	5-319	66	166-4028	634
8	9-111	27	9-52	25	19-156	67	15-314	108	18-130	53	9-268	58	148-4073	836
9	11-98	23	9-37	13	20-116	41	13-201	106	10-92	33	11-218	58	80-2664	1094
10	11-45	30	7-46	17	18-193	48	29-333	108	11-115	46	4-342	53	116-3847	915
Overall	6-126	27	5-103	21	5-416	50	10-468	116	8-843	47	3-639	55	80-7946	1080
(Left)														
1	27-86	70	15-72	28	13-204	45	133-284	170	25-198	112	36-120	61	597-4702	1519
2	8-29	13	6-14	8	9-29	16	18-109	52	6-25	16	13-94	48	490-1428	1150
3	29-44	30	14-50	17	23-132	30	99-183	147	14-124	26	33-106	84	707-7945	2179
4	6-25	14	5-10	8	8-27	15	23-143	84	5-45	22	10-130	41	304-3522	2012
5	19-61	33	16-29	26	30-78	42	122-151	133	24-73	31	15-91	46	2215-3953	2748
6	27-81	31	13-37	23	24-85	44	80-129	127	15-80	38	15-132	35	891-2777	1208
7	22-40	23	8-28	14	18-76	28	44-144	105	11-71	20	15-79	48	569-3685	756
8	19-24	22	6-27	9	19-72	19	14-168	144	12-67	20	13-214	91	1079-2697	1818
Overall	6-86	30	5-50	20	8-204	36	14-284	133	5-198	28	10-214	54	304-7945	1925

Table V (Con'd)

	Lung Segment	Cu		Zn		Mg		Ca	
		Range	M	Range	M	Range	M	Range	M
Right	1	44-344	137	74-20,806	897	1,557-18,814	8,588	11,383-116,883	31,123
	2	23-141	93	40-4,081	795	1,056-15,279	7,694	4,037-132,069	21,418
	3	43-437	120	51-7,438	798	3,332-17,117	8,436	12,175-146,224	23,815
	4	47-227	103	35-5,330	885	4,509-18,699	8,776	15,524-88,261	39,490
	5	57-234	180	93-2,505	878	5,039-19,019	9,544	11,856-166,143	32,426
	6	59-359	108	36-9,548	822	4,714-84,949	8,918	15,309-69,438	23,197
	7	36-265	131	63-2,725	885	5,442-107,200	8,655	12,368-66,496	36,745
	8	36-217	121	65-6,444	866	5,303-23,368	8,559	13,499-162,962	22,041
	9	40-308	113	66-12,139	614	4,962-18,975	9,108	16,470-215,300	30,210
	10	38-347	107	69-8,864	862	1,216-19,230	9,144	15,475-148,032	31,643
	Overall	23-437	116	36-20,806	885	1,056-107,200	8,865	4,037-215,300	29,945
Left	1	64-106	99	30-1,039	821	6,033-8,314	6,949	12,893-19,745	14,267
	2	54-124	92	32-195	195	6,541-7,556	7,141	16,146-53,040	37,358
	3	94-186	128	41-1,584	421	6,132-91,805	7,339	12,925-91,805	17,826
	4	32-102	80	16-1,037	92	2,689-23,924	10,572	6,591-34,501	22,363
	5	39-107	70	33-998	140	7,580-19,549	10,830	19,549-42,565	24,841
	6	43-148	103	44-1,095	71	9,077-17,426	8,930	15,452-31,320	23,258
	7	38-110	88	31-950	67	6,953-18,776	8,034	17,268-46,982	28,204
	8	36-243	85	44-515	73	7,014-21,968	7,114	15,196-40,717	29,969
	Overall	32-243	95	16-1,584	167	2,689-91,805	8,482	6,591-91,805	26,522

Table VI

Concentration of trace elements in scalp hair, pubic hair and lung

Metal	Sample Location	Lung No. 77	78	11	13	19	85	64	99	100	4	12
Pb	Scalp Hair (µg /g hair)	<16.8	504.0	1.2	<18.2	< 1.8	3.5	2.2	1.3	1.5	< .3	11.2
	Pubic Hair (µg /g hair)	31.3	<101.0	<5.0	138.0	<21.2	< 1.2	2.4	3.8	2.3	<1.8	44.4
	Lung (µg /g tissue ash)	80.5	53.0	52.5	30.9	22.3	75.9	23.9	50.5	47.2	19.1	48.3
Cu	Scalp Hair (µg /g hair)	<166.7	400.0	13.3	272.7	17.9	14.1	9.9	14.9	9.4	10.4	22.5
	Pubic Hair (µg /g hair)	468.8	101.0	50.3	61.3	<212.8	18.2	14.1	22.9	12.0	27.5	119.0
	Lung (µg /g tissue ash)	101.7	114.2	56.9	70.8	260.6	67.2	90.9	121.5	104.1	92.7	109.1
Zn	Scalp Hair (µg /g hair)	66.7	320.0	171.9	291.0	150.5	409.8	118.7	183.2	157.2	214.7	111.9
	Pubic Hair (µg /g hair)	593.8	282.8	241.2	98.2	127.7	191.7	130.2	142.8	140.6	801.5	44.4
	Lung (µg /g tissue ash)	126.8	85.8	149.6	70.6	2159.7	7418.9	50.5	89.0	77.2	801.3	84.5
Cd	Scalp Hair (µg /g hair)	< 1.7	< 4.0	< .1	< 1.8	< .2	.4	.5	.3	.1	.1	.6
	Pubic Hair (µg /g hair)	< 1.6	< 1.0	< .5	< .6	< 2.2	< .1	.2	.1	.1	< .2	< .8
	Lung (µg /g tissue ash)	13.9	33.3	14.0	64.9	11.7	42.9	112.6	95.4	103.2	57.6	26.6
Ni	Scalp Hair (µgr/g hair)	<166.7	<400.0	< 6.6	<181.8	<17.9	< 2.7	7.8	< 5.0	< 4.8	<3.3	<6.4
	Pubic Hair (µgr/g hair)	343.8	<101.0	<50.3	< 61.3	389.4	<12.1	<4.7	< 5.1	<6.0	<18.2	<79.4
	Lung (µgr/g tissue ash)	26.8	23.0	16.0	25.4	23.9	23.2	32.5	12.2	21.6	23.1	43.0

4. Discussion

The concentrations of metals in the ash from the bronchopulmonary segments of the lung indicate that certain elements are not uniformly distributed and that metals in both left and right lungs with the exception of calcium, magnesium and cadmium were to varying extents, present in greater concentration in the apical tissue. This agrees with the findings of Molokhia and Smith [13] that trace elements are present in higher concentrations in apical tissue. Nevertheless this should be interpreted with caution.

Trace element concentrations in lung may be expressed in several ways. The total weight of an element might be misleading as the weights of essential metals present (Ca, Na, K, etc.) might be expected to vary with lung size and contaminating metals likely to be present in larger amount in lungs of greater capacity. If the metal content is expressed as percentage wet weight, errors arise due to oedema and blood clots. Concentrations expressed as a percentage of dry lung weight require uniform methods of drying and local disease (e.g. emphysema or fibrosis) might lead to articifially high or low dry lung weights. While it is still our intention to examine our data in the above manner, in this study we chose to describe the concentrations of metals in lung as µg metal/g lung ash. The results indicate that concentrations expressed in this way must also be interpreted with caution, as aging and calcification of diseased areas of lung can produce higher weights of lung ash from certain regions of the lung lowering the concentration of other elements. This problem probably exists even when whole lungs are used for analysis.

Preliminary data presented in this report indicate that metals can be detected in the hair of the general population, but the extent of the scatter of the results obtained to date suggest that hair is unlikely to serve as a suitable method of surveying the general population for exposure to trace elements present in air pollutants.

Acknowledgements

We acknowledge with thanks the technical assistance of Miss Janet Palser. This study was undertaken with the help of a grant from the Quebec Department of Municipal Affairs.

REFERENCES

1 KOCH, H.J.Jr., SMITH, E.R., SHIMP, N.F., CONNOR, J., "Analysis of elements in human tissues", Cancer, 9, 499 (1956).

2 Report of Comittee II on permissible dose for internal radiation, ICRP Publication, (1959), Pergamon Press, London (1960).

3 ROSSITER, C., RIVERS, D., BERGMAN, I., CASSWELL, C., NAGELSCHMIDT, H., "Dust content, radiology and pathology in simple pneumoconiosis of coal workers" (Fourth Report), Inhaled Particles and Vapours, ed. C.N. Davies, 419, Pergamen Press, Oxford, England (1967).

4 KEENAN, R.G., CRABLE, J.V., SMALLWOOD, A.W., CARLBERG, J.R., "Chemical composition of the coal miner's lung", American Ind. Hyg. Assoc. J., 392 (1971).

5 DIXON, J.R., LOWE, D.B., RICHARDS, D.E., CRALLEY, L.J., STOKINGER, H.E., "The role of trace metals in chemical carcinogenesis: Asbestos cancers", Cancer Research, 30, 1068 (1970).

6 MULAY, I.L., ROY, R., KNOX, B.E., SUHR, H.N., DELANEY, W.E., "Trace-metal analysis of cancerous and non-cancerous human tissues", J. Nat. Cancer Inst., 47, 1 (1971).

7 GIBBS, G.W., LACHANCE, M., "Dust exposure in the chrysotile asbestos mines and mills of Quebec", Arch Environ Health, 24, 189 (1972).

8 GIBBS, G.W. "Qualitative aspects of dust exposure in the Quebec asbestos mining industry", Inhaled Particles III, Ed. H.A. Walton, Vol. II, 783, Unwin Bros. Ltd., London, England (1971).

9 EL-DAKHUKHNY, A.A., EL SADIK, Y.M., "Lead in hair among exposed workers", Arner Ind. Hyg. Assoc. J., 33, 31 (1972).

10 PETERING, H.G., YEAGER, D.W., WITHERUP, S.O., "Trace metal content of hair I. zinc and copper content of human hair in relation to age and sex", Arch. Environ Health, 23, 202 (1971).

11 DIEM, K., Documenta Geigy, scientific tables, 6th ed., Geigy Pharmaceutical Co., Ltd., Manchester, England (1965).

12 TIPTON, T.H., SHAFER, J.J., "Statistical Analysis of lung trace element levels", Arch Environ Health, 8, 58 (1964).

13 MOLOKHIA, M.M., SMITH, H. "Trace elements in the lung", Arch. Environ Health, 15, 745 (1967).

TRACE METAL CONTENT IN HAIR AND THE LEVELS OF 5-HIAA IN THE URINE OF POPULATION EXPOSED TO LEAD

B. STANKOVIĆ, M. STANKOVIĆ, S. MILIĆ,
Z. KORIĆANAC, LJ. MILOVANOVIĆ, M. DUGANDŽIĆ

Institute of Occupational and Radiological Health, Belgrade, Yugoslavia and Institute of Inorganic and Analytical Chemistry, Faculty of Pharmacy, Belgrade, Yugoslavia

ABSTRACT

The aim of this paper is to present our first results, as a part of a long-term project, on trace metal content of hair in human population exposed to different pollutants, including our observations of 5-HIAA excretion in lead exposure.

The study population consisted of four groups, representing four levels of lead exposure: without exposure, urban level of exposure - low level, intermediate exposure of people living around lead plant, and high level of exposure of lead workers. Absorption of lead in hair was very marked and gradually increased with the degree of exposure, from 3.76 to 71.90 µg/g. Lead and cadmium in hair, as non-essential elements, of unexposed and exposed people showed rather good degree of association of the metals. Our results show that the mean hair Pb level and also Cd level did reflect community exposure and might be a useful biotoxicological index of a prolonged exposure. The contents of the two essential trace elements, Cu and Zn, did not differ so significantly between farmers, city residents, the subjects living near lead plant and lead exposure workers.

The study of 5-HIAA, as the end metabolite of minor pathway of tryptophan, shows the increased levels of the excretion in

Preceding page blank

the group of 120 exposed inhabitants. The results of our study demonstrated that the determination of 5-HIAA in the urine can be used as a useful and additional test for better assessment of the environmental lead exposure.

1. Introduction

Epidemiological data suggested that, in the inhabitants living in the vicinity of a non-ferrous metals smeltery and refinery, the exposure to a mixture of heavy metals is quite possible.
Recently, attention is paid to the determination of various trace metals in hair as an index of a prolonged exposure. Hair has long been recognised as a metal-containing metabolic end product /1/. Also hair, by some authors /1,2,3 and 4/, better reflect the total body pool of some elements than either blood or urine, and this tissue may prove a practical dosimeter for metallic environmental pollutants.
In this study, hair analysis has been applied to two classes of elements: the essential nutrients, such as zinc and copper, and elements such as lead and cadmium for which no evidence of essentiality has been found.

Our findings of the significant contents of lead in the hair of the inhabitants living near a lead-zinc plant suggested the examination of eventual derangements in the metabolism of some amino acids. From that reason the urinary excretion of 5-hydroxyindolacetic acid /5-HIAA/ has been studied in a group of people from that region.

2. Materials and Methods

The study population for trace metals in the hair consisted of male and female of three different groups, and one group of workers mostly exposed to lead:

1/ a group of peasants far from any pollution /30 cases/,
2/ a group of residents of Belgrade /40 cases/,
3/ a group of inhabitants living at least 10 years in the vicinity of a lead smelting plant /50 cases/, and
4/ a group of workers from mentioned lead plant/50 cases/.

As a sensitive, accurate and relatively interference-free technique, atomic absorption allows rapid analysis for trace elements. Therefore, in our study hair analysis were done by atomic absorption spectrometry,using a Unicam SP 90A, Ser.2. Virtually, all of the samples were collected during the fall of 1973 and the last two weeks of February 1974. Hair samples were collected in the small plastic bags, numbered and brought to the Institute of Occupational Health Lab. for analyses. The special precautions and washing with 1% detergent solution,warm deionized water and 1% HNO_3 were taken to avoid trace elements contamination. Hair samples were prepared in 2% nitric acid for atomic absorption determination of metals after wet acid-digestion with nitric acid and hydrogen peroxide.

The concentrations of 5-HIAA were determined in the fresh urine samples by a spectrofluorometric method /5/. From the same urine samples the determination of delta-aminolevulinic acid /ALA/ has been also carried out by Grabecki method /6/.

3. Results and Comments

Studied population consisted of four groups, actually ranking four levels of lead exposure: 1st group - without exposure, 2nd group - low, urban level of exposure, 3rd group - intermediate exposure in the settlements surrounding lead plant, and 4th group - high exposure of lead workers.
The results of trace metal analyses in hair are summarized in table I. The arithmetic means with standard deviations of lead, cadmium, copper and zinc were presented for each group.

Table I. - Trace metal content in hair, µg/g
The mean values with standard deviations

Group*	Lead		Cadmium		Copper		Zinc	
	mean	s	mean	s	mean	s	mean	s
1st	3.76	2.30	0.22	0.17	9.54	3.15	153	51.5
2nd	7.16	4.41	0.30	0.22	9.28	2.76	137	41.1
3rd	33.13	17.84	0.33	0.14	7.71	2.90	154	49.8
4th	71.90	30.80	0.78	0.82	10.70	3.52	158	39.6

* - For the groups see the chapter: Materials and Methods
s - Standard deviation

The mean values for the two non-essential and toxic trace elements, Cd and especially Pb, shown differences between groups, and were in accord with exposure rankings for Pb and Cd. On the other hand, means for the two essential trace elements, Cu and Zn, did not differ significantlly between people in village, city, around lead plant,and the lead workers.

Uptake of lead in hair was very marked and gradually increased with the degree of exposure. From that reason the data of lead in hair are presented separately in table II.

Table II. - Lead in hair, µg/g

Group	Number of cases n	Range		Arithmetic mean $\bar{x}$	Standard deviation s
		min	max		
1st	30	1.2	10.0	3.76	2.30
2nd	40	1.7	18.5	7.16	4.41
3rd	50	5.2	78.0	33.13	17.84
4th	50	20.0	163.0	71.90	30.80

The mean values of lead in hair of unexposed population were 3.76; than 7.16 of urban population; 33.13 of inhabitants living near lead smelting plant and 71.90 µg/g of lead exposed workers. The calculation of t-test of the arithmetic mean values between all groups revealed the highly significant differences /$P < .001$/, except between the 1st group/farmers/ and the 2nd group /urban population/, where it was only significant /$t = 2.50$; $P < .05$/.

Lead and cadmium in the hair of unexposed and exposed people showed rather good degree of association of the metals. The levels of cadmium in all groups and their means were lower than those previously reported /1, 7, 8/.

Scalp hair has several of the characteristics of an ideal tissue for epidemiologic study and it is painlessly removed, normally discarded and easily collected. Hammer and co-workers /7/ in their study minimized possible effects of age, sex, hair color, varying hair length and personal chemical treatments. Our study shown, that despite of some problems, the mean hair lead level and also cadmium level did reflect community exposure and therefore might be an useful biotoxicological index of a prolonged exposure.

The results of metal contents in hair obtained in a group of inhabitants living in the vicinity of a lead smelting plant, and the concentrations of lead in air /1 - 80 µg per m^3/ of that environment, suggested further investigation. The studies of 5-HIAA excretion as the end metabolite of minor pathway of tryptophan, parallel to the ALA excretion in the urine/as an indicator of lead absorption/ were carried out. A larger, homogeneous group of 120 persons from that area has been examined. As the control, a group of 30 citizens without known lead exposure has been also examined. The results are shown in table III.

Table III. - Excretion of 5-HIAA and ALA

Biological parameters	Exposed group		Control group	
	mean	stand. deviation	mean	stand. deviation
5-HIAA, mg/l	7.35	2.32	2.86	1.21
ALA, mg/l	9.20	8.65	5.21	2.48

The increased levels of 5-HIAA in the exposed persons were evident. The difference between the arithmetic means of urinary 5-HIAA of exposed and unexposed population was statistically significant.

5-HIAA has been found in the urine presumable as the end-product of the action of monoamine oxidase /9/ on 5-hydroxytryptamine /serotonin/, which plays a rôle as an important physiological agent. In the urine of normal human subjects the 5-HIAA is present in small amounts, a few miligrams per day.

The results of our study demonstrated that lead interferes /possibly/ in some manner with the enzymatic degradation of serotonin - in the long run of tryptophan. Consenquently, it seems that 5-HIAA excretion can be used as an additional and simple biochemical test for obtaining a more complete picture in favour of the environmental lead exposure.

References

1. Schroeder,H.A., Nason,A.P.:"Trace metals in human hair", J. Invest. Dermatol., 53, 71 /1969/
2. Yurachek,J.P., Cemena,G.G., Harrison,W.W.: "Analysis of human hair by spark source mass spectrometry", Anal. Chem., 41, 1666 /1969/
3. Kyle,R.A., Pease,G.L.: "Hematologic aspects of arsenic intoxication", New Eng. J. Med., 273, 18 /1966/
4. Kopito,L., Byers,R.K., Schwachman,H.: "Lead in hair of children with chronic lead poisoning", New Eng. J. Med., 276, 949 /1967/
5. Kimura,Y., Arai,Y., Shimatavi,J., Hirona,H.: "Determination of 5-hydroxyindolacetic acid in urine", Arerugi, 16, 463 /1967/
6. Grabecki,J., Haduch,T., Urbanowicz,H.: "Die einfachen Bestimmungsmethoden der Aminolävulinsäure im Harn", Int. Arch. Gewerbepath. Gewerbehyg., 23, 226 /1967/
7. Hammer,J.D., J.F.Finklea, R.H.Hendricks, C.M.Shy, R.J.M. Horton: "Hair trace metal levels and environmental exposure", Amer. J. Epidem., 93, 84 /1971/
8. Petering,H.G., Yeager,D.W., Witherup,S.O.: "Trace metal content of hair", Arch. Environ. Health, 27, 327 /1971/
9. Sjoerdsma,A., Smith,T.E., Stevenson,T.D., Udenfriend,S.: Proc. Soc. Exp. Biol.and Med., 89, 36 /1955/

2293

PANEL DISCUSSION

Preceding page blank

SUMMARY OF DISCUSSION

WEBER (Yugoslavia)

The unifying themes in this session will be singled out as follows: hair, lungs and to a minor extent other tissues as well as methods of analysis with special reference to atomic absorption and spectrometry but we will limit the discussion to hair and lungs. We proposed the following order:

Hair:

a) can hair be used for the measurements of trace elements, exposure, or absorption; what are its advantages and disadvantages?

b) How do elements in other tissues correlate with the levels in hair?

c) How are trace elements distributed in hair, for example along its length?

Lungs:

a) What is the value of analysing lungs for trace elements? Do they reflect trace element exposures?

b) How are trace elements distributed in the lungs?

c) How should the results of element analysis be expressed, for instance, μg/g, ash; μg/g, wet tissue; or some other dimension?

Turning now to the first question, can hair be used for the measurement of trace element exposure or absorption? What are its advantages and disadvantages?

Preceding page blank

DISCUSSION

VUORI (Finland)

Everyone knows the advantages of hair as biopsy material but I am sure that we do not know all the disadvantages that this material has. For instance it was not until at the end of last year that Hambidge showed that the copper concentration of hair depends even on sampling technique, so that the distal parts of hair had more copper than the proximal parts. Further an unsolved problem is the treatment of hair before analysis, dozens of different procedures are published in literature. In our case we had to pre-wash our hair samples, because in some cases they were badly contaminated by blood (samples taken from persons having died of head fractures) and this was a phase that we had to add to those previous methods. We prefer both organic and detergent agents for washing hair samples before ashing procedure.

GIBBS (Canada)

Dr. Vuori has drawn attention to the problems of sampling and washing hair before analysis. The turnover rate of hair is also likely to limit its usefulness for assessing long-term exposure. For many years the analysis of hair and nails has been accepted as a method of demonstrating the ingestion of arsenic compounds. It is not yet clear how the other trace elements we are discussing enter the body or become concentrated in hair. Elements may be absorbed through the gastrointestinal tract, or through the lungs, or through both, depending on the element in question. In addition, metals might be adsorbed to the outer surface of the hair. These factors must be taken into account if hair is to be useful for the evaluation of either exposure or absorption.

BENINSON (Argentina)

Hair measurements could be indicators of intake over a given period, even if concentrations in hair do not correlate with concentrations in tissues. This can be due to different retention functions and residence times, and different characteristic integrating times of each integrator.

GIBBS (Canada)

This is a very valid point and Dr. Stankovic has shown quite clearly that the concentrations of lead in hair can be used for such purposes. In our very preliminary report we indicated that trace element concentrations in hair did not appear to be related to the concentrations in lung. This may certainly have been because elements had been removed from the lung or because the elements present in the hair entered the body by a route other than through the lung.

PISCATOR (Sweden)

1. In the case of cadmium, it is impossible to distinguish between endogenous and exogenous cadmium in hair. Cadmium from air will be as firmly bound as cadmium from the body.

2. Metals such as Cd deposited in hair will be absorbed at different rates dependant on the pH of the hair.

WEBER (Yugoslavia)

This worry does not apply to cadmium only, it applies to lead as well. Perhaps we have an extreme case in occupational health problems, but lead is ubiquitous and one can just by washing hair, or just walking on the street get some lead deposited on the hair and it is a question whether it can be removed by ordinary washing or not. Another point that I want to make is: what does washing of hair before analysis, really mean? How much lead or cadmium or any other trace elements are removed. Some of the metals are built into the structure of hair, hair being a protein of the keratine type, where sediments in general are quite strongly bound to different groups in the structure of the protein. On the other hand some people wash hair before the analysis in 1% nitric acid, and I am quite sure that under these conditions part of the absorbed metals will be removed.

BERNSTEIN (Canada)

In testing native Canadian Indians for mercury levels, we found they were often more hesitant to give up a strand of hair than to allow a specimen of blood to be withdrawn.

Has anyone had experience in the determination of hair selenium levels?

CLEMENTE (Italy)

We measured in Italy the Se hair concentration in three different population groups exposed to quite different Hg contamination. Any significant difference in the Se hair concentration was observed as a function of the Hg level in hair. The average Se concentration in the hair of the three population groups was about 0.1 - 0.3 ppm. These data on Se will be published in the near future.

HINE (U.S.A.)

The skill of the analyst in determining small concentrations of metals in the hair has led to certain problems in diagnosis and therapy. The findings of elevated levels of metals in the hair has resulted, on the part of some physicians not skilled in environmental and occupational mechanisms, in the employment of chelate therapy in an attempt to reduce the presumed increased body burden of that metal. The analyst should lend his skills to a proper interpretation of the significance of the findings. Certainly therapy should not be administered unless there are significantly elevated concentrations in the blood and clinical signs and symptoms confirmatory of a diagnosis of metal intoxication.

KJELLSTROM (Sweden)

It is very important in comparisons of hair levels of metals with the levels in other tissues to define what type of relationship one is studying. As Dr. Beninson indicated you have to define if you are trying to evaluate the hair levels as an indicator of recent exposure, concentration in critical organ or total body burden. In the case of cadmium I believe the reports at this Symposium and earlier reports show that hair is not useful as an indicator of any of these variables. Nordberg has shown with radioactive cadmium no correlation between cadmium in blood and hair, in mice. Watanabe in Japan has not found hair to be useful in evaluating exposure level in an area where water but not air was polluted.

KREUZER (B.R.D.)

Wenn Haare Schwermetalle anreichern (z.B. Pb, Cd) wäre es im Interesse der Interpretation und Vergleichbarkeit der erhaltenen Ergenbnisse wichtig in etwa gleich alle Haare zu untersuchen. Das dürfte in der Praxis auf gewisse Schwierigkeiten stossen, da selbst eng benachbarte Haare recht unterschiedlichen Alters sein konnten. Dieses Problem liesse sich durch Entnahme grösserer Proben Haare lösen, doch laüft dies wieder den Bemühungen einer Entnahme möglichst kleiner Proben zuwider.

When hair is burdened with heavy metals (e.g. Pb, Cd) it would be of advantage for the interpretation and comparison of the results obtained if all the hair was examined equally; this would be difficult in practice as even neighbouring hairs can vary considerably in age. This problem could be solved by taking greater samples of hair, nevertheless this would be contrary to the effort to keep the samples as small as possible.

WEBER (Yugoslavia)

The speakers refer to the question, how are trace elements distributed in hair, for example along its length; now we have heard that also there could be some differences between two adjacent hairs. What about a single hair along its length. Recently I received a communication from Columbia University in New York where they told me that there is a maximum concentration at about 7 cm from the scalp regardless of the age or of anything else, and another peak if I remember correctly at 23 cm. I just could not interpret that and I wonder if anyone has some experience in this respect.

TRUFFERT (France)

La fixation des oligo-éléments dans les cheveux semble se faire sur les groupements-SH libérés par la réduction de la cystine en cystéine. On peut réaliser une telle fixation in vitro et après réoxydation qui régénère la kératine, on ne peut distinguer l'oligo-élément ainsi fixé de celui qui existait in vivo. On peut donc penser que la fixation des oligo-éléments dans les cheveux se fait avec la croissance des cheveux, en fonction de leur teneur dans l'organisme à ce moment.

Trace elements appear to be fixed in the hair in the SH-groups released by the reduction of cystine to cysteine. This fixation can be achieved in vitro and, after the keratin has been regenerated by reoxidation, it is impossible to distinguish a trace element fixed in this way from one existing in vivo. It may therefore be assumed that the fixation of trace elements in the hair is concurrent with the growth of the *hair and proportionate to the levels of trace elements in the body at a given moment.*

WEBER (Yugoslavia)

This is quite correct, metals can be fixed either through metabolic processes or from the outside. It is the same thing as in dying wool, if you like. But the fact that in different subjects there is always a peak at 7 and 23 cm starting from the scalp intrigued me.

BRAETTER (B.R.D.)

Bei unseren noch laufenden Untersuchungen von Haaren mehrerer peruanischer Mumien, haben wir ebenfalls ein signifikantes Maximum der Spurenelementkonzentration im Abstand von 6 bis 8 cm von der Haarwurzel festgestellt. Eine Erklärung dieses Effektes haben wir auch noch nicht gefunden.

We are at present carrying out researches on the hair of several mummies from Peru. We too have found a significant maximum of the trace elements concentration at a distance of 6 to 8 cm. from the hair root. We have not yet found an explanation for this effect.

WEBER (Yugoslavia)

Having exhausted the question of hair we move on to the lungs. What is the value of analysing lungs for trace elements Do they reflect trace element exposures?

GIBBS (Canada)

The analysis of lungs for trace elements is time consuming and the reasons for carrying out such analyses should be clearly defined. We know that airborne particulates containing trace elements enter the lungs, some are retained, some dissolve and are absorbed, and other particulates may be removed by other mechanisms. For certain insoluble particulates penetrating deeply into the lung, the lung might act as a collector and there may be some instances where trace element analyses of lung may be useful.

In order to study specific problems such as the relationships between trace elements and lung cancer, there may be some value in measuring the trace element distribution within the lungs of cases and suitably matched controls. The analysis of lung to monitor the trace element exposure of the general population is questionable, and I suspect that such analyses will not prove to be very useful. We are currently studying this problem and hope to examine the relationship between trace elements in lung and community air. The likelihood of finding a strong association is slight because of the removal processes mentioned above, and because of the mobility of the population.

WEBER (Yugoslavia)

For epidemiological studies there is an additional problem of biopsy.

GIBBS (Canada)

Yes, this can be a serious problem. It is necessary to rely on the collaboration of the pathologist and pathology technician, and often whole lungs are not available because segments are needed by the hospital for other purposes When the specimen is taken, it is important to avoid contamination by talc, etc., from surgical gloves, washing of the specimen and fixing in formalin. These two latter processes may add or remove trace elements. Many of the problems facing the investigator are not related to the analytical methods but to the collection and handling of the specimen. The investigator is able to supervise closely the analytical stages but often has to take specimen collection on trust.

WEBER (Yugoslavia)

Touching on the last question, how should the results of trace element analysis be expressed, for example, µg/g ash, µg/g wet tissue? This applies not only to lung but to other tissues as well, but what troubles me is: what does it really mean to have sophisticated analytical procedures working hard to try to get results with 3 or 4 significant figures when the actual concept of the tissue as such is not defined. Is it better to express it as dry or wet tissue no matter how wet or dry it is, if we express it per gram of ash has this tissue been calcified or are some other problems involved in the tissue depending on the height and size of the person in question, for instance?

KJELLSTROM (Sweden)

If space is available I think that both wet weight, dry weight and ash weight should be reported in order that studies should be comparable.

PITTWELL (U.K.)

It is my experience when analysing other body tissues than those discussed (lymph glands, muscles and body fat) for trace elements, that there are problems of water loss which start the moment the tissue is removed from the body. If as in the case of my own study the trace elements may be present as inorganic inclusions, it is essential to know the relation to the organic content of the tissue, then the only safe way of returning results is to determine with respect to wet, dry and ash weights. This can be done by quoting the drying loss as percentage, the ash percentage and the analysis of the ash for trace elements. In some instances a relation to carbon content can be used as well, but this is harder to determine.

UNTERSUCHUNG DER GESUNDHEITLICHEN WIRKUNGEN
HEALTH EFFECTS STUDIES
ETUDES DES EFFETS SUR LA SANTE
STUDI DEGLI EFFETTI SULLA SALUTE
ONDERZOEKINGEN NAAR GEVOLGEN VOOR DE GEZONDHEID

Vorsitzender - Chairman - Président - Presidente - Voorzitter

H.E. GRIFFIN (U.S.A.)

Stellvertretender Vorsitzender - Vice-Chairman - Vice-président
Vicepresidente - Vice-Voorzitter

A.E. MARTIN (U.K.)

HEALTH EFFECT STUDIES - NOW AND IN THE FUTURE

LARS FRIBERG

**Department of Environmental Hygiene, The Karolinska Institute,
and the National Swedish Environment Protection Board, Stockholm
Sweden**

ABSTRACT

Health effects, ranging from slight annoyance reactions at the one extreme and death at the other, can be studied toxicologically and epidemiologically. Toxicological studies must elucidate what metabolites are formed by a given substance and what mechanisms of action it has in nature and in the body. The ultimate aim of such studies is to obtain a dose-response curve, which is often difficult. Much valuable epidemiological and toxicological data are lost to the researcher simply because industrial health officers do not use their resources for the collection and compilation of such data or, if they do, they must often keep the results confidential. The TLV values for industrial exposure must be reevaluated since they do not always protect the worker. Differences in prevalence of disease among countries both from environmental and industrial agents have not yet been satisfactorily accounted for. Epidemiological base registers should be initiated or, when they exist, expanded, for example through material collected from questionnaires. Factors of self-selection must be given due regard when data on voluntary exposure to harmful agents, e.g. cigarettes, are to be interpreted. Studies on twins which are discordant as to the exposure to a certain agent may be fruitful in this respect. Vital statistics, cancer registries and hospital records should be given more entrance into epidemiological studies. A plea is made for more extensive training of epidemiologists and toxicologists.

Preceding page blank

Health effects cover a wide range of biological responses. Death and disease represent one extreme of the whole spectrum of response. At the other extreme will be found physiological and other changes of uncertain significance, e.g. increased body burdens of pollutants as well as annoyance reactions due to bad odors or noise. Health effect studies usually involve humans or animals but may also be carried out in vitro using different cell systems. They are as a rule of multidisciplinary nature, utilizing medicine, chemistry, physics or behavioral sciences.

The two major approaches are toxicology and epidemiology. Toxicological studies use animals of different species. Such studies may range from more conventional determinations of acute and chronic toxicity to sophisticated studies of metabolism, mutagenic, carcinogenic, and teratogenic effects. Epidemiological studies on the other hand aim at mapping biological effects as they occur in reality, meaning that primarily studies on humans, often large groups, have to be embarked upon.

When new substances are intended to be brought to market, the first step will be toxicological studies. Even if such studies are carried out, using all available techniques, data from animal experiments cannot easily be extrapolated to humans. Epidemiological studies are therefore often imperative in order to ascertain that the results from toxicological studies on a given substance hold true. Furthermore, epidemiological studies are indispensable as a form of health surveillance of trends in incidence of disease and mortality in order to detect at a very early stage health effects where no suspicion towards a specific exposure has arisen.

Scientific and practical requirements differ for different types of health effects. The basis for study is, however, always a need for understanding the mechanism behind possible effects and the documentation of the dose-response relationships. Several problems will come up which often will motivate massive efforts, the magnitude of which will depend on inter alia the risks the community is willing to take and the number of people who may possibly be exposed.

There are many examples of the difficulties in carrying out health effect studies. Here may be referred to the fact that despite overwhelming evidence of a causal association between cigarette smoking and lung cancer, this effect has not been possible to reproduce unequivocally in animals.

It goes without saying that even if governmental and private support for toxicological and epidemiological evaluations should grow dramatically, only a small part of the ever-increasing numbers of chemical substances brought to market can be studied in a satisfactory way. This will be all the more obvious when possible interactions between pollutants, often with potentiating effects, are considered. The toxicity, not only of the substance itself, but also of its metabolites, must be investigated. Metabolism may vary within a species and among different species. This, together with different toxicity or different exposure routes, complicates further any toxicological evaluation.

Mercury gives a good example of the complexity of the toxicological situation. The tragic incidences of mercury poisoning via fish in Minamata and Niigata in Japan and recently, on a large scale via a seed dressing in Iraq, are well known. Those mass outbreaks were caused by methyl mercury, an organic mercury compound which is one of the most toxic mercury compounds known, also involving a high risk for the fetus. It would be a serious error, however, to conclude that other organic mercurial compounds, like phenyl mercury and methoxyethylmercury, will also have a similar toxicity. Unlike methyl mercury, these organic compounds are readily broken down within the body, forming mercuric ion, and the toxicity is lower and more similar to the one experienced after exposure to mercuric mercury. Metallic mercury, on the other hand, has a toxicity which differs from that of methyl mercury, other organic mercury compounds and mercuric mercury salts. After absorption, it exists for a short time as physically dissolved mercury vapor in the blood, and in this form it easily penetrates the blood-brain barrier and the placenta. As for accumulation and excretion of absorbed mercury, methyl mercury has a biological half-time in all organs of on an average 75 days. The biological half-time of inorganic mercury is only a couple of months in the blood, while, when it has reached the brain, the half-time will be in the order of years. As regards the toxicological evaluation of mercury, the possibilities of methylation in nature, meaning that mercury can be transformed into methyl mercury, must also be borne in mind.

When it comes to the relation between dose and response (Dose-response curves) the magnitude of our efforts will depend on the risks we are willing to take as basically it will be virtually impossible to show a true no-response dose. Not even for cigarette smoking, with all the millions of people studied, do we know the exact relation when it comes to a low exposure. We know that lung cancer is strongly and causally associated with smoking but we cannot quantify the risks, if any, of smoking say one or two cigarettes a day. It could be argued that this is of minor importance as from the health point of view a proper decision taken by administrators could be to prohibit smoking. Apart from the fact that this for several reasons is not possible, and could lead to several very undesirable effects due to the addictive nature of the smoking habit, the question has an obvious bearing in relation to passive smoking, meaning the tobacco smoke that nonsmokers are exposed to. We know that concentrations of particulate matter in rooms where several smokers are together easily will reach concentrations in the mg range, far above concentrations of particulate matter which by the WHO have been considered to give rise to health effects. One problem is that a combination of particulate matter and sulfur oxides was considered in the WHO criteria. Tobacco smoke consists of particulate matter together not with sulfur oxides but with a large number of other gases. There are some data from England which are highly suggestive of respiratory effects in young children due to passive smoking. More extensive data are needed before definite conclusions can be drawn, however. To come up with dose-response relations for passive smoking not only for the average adult but also for children and people with pre-existing disease would involve large effort, taking into account among other things that there are reasons to believe that tobacco smoke as related to passive smoking would differ from freshly produced tobacco smoke.

I shall now turn to a few questions in connection with industrial exposure to chemical substances. It is customary in health effect studies to consider separately studies which are based on industrial exposure, exposure via food, and exposure within the general environment, e.g. ambient air and water. Admittedly there are large differences between such different exposure situations both in regard to the magnitude and the route of exposure. Furthermore, the populations exposed may differ considerably in relation to time of exposure and sensitivity to the different agents.

On the other hand, it is obvious that very often our best opportunities to get information on effects of toxic substances are found within industries, particularly as the exposures often are so much higher there. It is also obvious that in the extensive criteria documents by the US Environmental Protection Agency much attention has been paid to results from industrial exposure. It is certainly most unfortunate that data from industrial exposures are so relatively scarce as they are considering the number of people who are exposed to different substances. It is the more unfortunate in view of the fact that the possibilities of making good studies within the general scope of the industrial health services are so enormous. The lack of data lending themselves to dose-response evaluations was pointed out by a Task Group on Metal Accumulation at a meeting in September 1972, for metals, but seems to be valid also for almost any other substances. It was then said that there is a lack of epidemiological data from populations with industrial exposure. This lack is even more striking in relation to the growing number of such studies on populations with general environmental exposure, which is usually at a much lower level. There is a need in industrially exposed populations for standardized, wherever possible collaborative, epidemiological studies, where cohorts can be followed in time and where groups can be related to each other.

The lack of published data from industrial exposure certainly is due to several reasons. Very often studies are not carried out at all within industries, responsible officers relying on recommended TLV-values, which, however, are notoriously unreliable and should be completely reevaluated. One recent tragic example concerns vinyl chloride, for which the TLV is definitely too high. It is set by the American Conference of Governmental Industrial Hygienists at 200 ppm (in Sweden set at 500 ppm) despite the fact that in the accompanying documentation for this value there are data which indicate toxic effects on the liver at concentrations even lower than 200 ppm. Now exposure to vinyl chloride is associated with liver cancer in humans.

In cases where industrial health studies are carried out there are examples showing that management is unwilling to release data which later can be used against them in connection with legal procedures. Furthermore, very often the number of people exposed within a given industry for a given substance may be small. This means that statistically significant effects, when comparisons are made against a control group, may not be detected even if such effects in reality exist. In order to show with reasonable assurance that a certain effect, also a very severe one, does not occur in an increased prevalence in an exposed group compared with a control group the study populations often have to be large. This could be accomplished if collaborative studies between industries were carried out even on a rather limited scale. To me, the question of increasing the number of studies, improving their quality and providing for their free publication has for the time being the greatest potential for epidemiological evaluations of toxic substances. This potential is valid not only for those who have the responsibility for protecting the industrial worker but also for other health agencies. Collaboration on all levels is necessary.

Collaborative efforts are also desirable on the international level. There are several examples where an effect in one country may not be reproduced in another country despite apparently similar exposure situations. This has been shown in connection with international studies of lung cancer and of cardiovascular disease. The reasons for differences in prevalence are not clear but cannot simply be explained by the occurrence of commonly recognized risk factors. There are other examples which show the opposite. I would like to refer to recent studies into the effect of aircraft noise reported at this symposium by a Swedish group. Despite rather large differences in cultural settings it seems as though when the proper exposure and effect parameters are used annoyance reactions due to aircraft noise are very similar for a given dose in Sweden, France, England and Japan.

For most epidemiological studies the aim will be to study individuals with known exposure situations and not only to carry out macroepidemiological studies monitoring exposures and effects without clear relation to each other. I would like to advertize here the possibility of using mail questionaires to a larger extent than hitherto. Certainly already by means of this simple tool a considerable amount of exposure data can be made available. This has been shown among other things in Swedish and US studies on twins and English, Norwegian, and US studies on immigrants. The Swedish and US data on twins included data on smoking habits, drinking habits, food and drug consumption, personality factors, occupation and exposure to air pollution. Such data may form the nucleus for an "epidemiological base register" as it is often too late to get such information at a later stage when one wants to correlate effects, e.g. disease, death, or annoyance reactions, with exposure data. It would be possible, on a global basis and for reasonable costs, to carry out such studies which would give much better possibilities in the future to interpret differences between different populations in morbidity and mortality rates.

For certain types of health effects studied group comparabilities between exposed group and controls are particularly crucial. This refers to comparison of groups who to some extent are self-selected. I am thinking of studies where smokers are compared with nonsmokers. There are good reasons to believe that a smoker does not become a smoker by chance only but that smokers and nonsmokers differ considerably in many other aspects than smoking habits. For example, it has been shown in Swedish studies that nonsmokers are registered in a nationwide alcohol registry to 10%, those who smoke between 1 and 10 cig/day to about 20% and those who smoke more than 10 cig/day to about 30%. Under such circumstances studies on twins discordant for the agent to be studied may be of particular value. Studies involving discordant monozygotic twins would keep genetic factors under complete control and it has also been seen that such pairs are more similar in relation to several confounding background factors.

Although it is obvious that epidemiological studies if possible should be of the prospective type where exposure and effects are studied on the individual basis other forms of health surveillance may also be of considerable value. I am thinking particularly of using data from vital statistics, cancer registries, hospital records. Such data will never be conclusive in themselves but may serve as early warning systems for health effects. Ideally such data should be linked with data from more conventional studies.

A question of particular importance refers to the training in toxicology and epidemiology. With very few exceptions there is a lack of toxicologists and epidemiologists. There is an extreme need for improving and expanding the training facilities both in individual countries and on an international scale. Not only are trained toxicologists and epidemiologists needed for carrying out toxicological and epidemiological studies; administrative bodies also need the advice of such personnel. The evaluation of scientific data from the literature, meaning working out criteria documents, is an extremely qualified task and can only be carried out properly by scientists who themselves are familiar with the research methods used.

DISCUSSION

LEHTO (Finland)

You mentioned that "management is unwilling to release data, which later can be used against them in connection with legal procedures".

How do you see scientist's role in this situation? Is it enough that we see ourselves only as specialist who answer only questions which are asked or put by administrators?

FRIBERG (Sweden)

This is first of all a question of education of management. They must learn that in the long run it is for their own benefit that data are published, as such information must be the basis for protective measures not only in the industries with which they are concerned but also in other industries. Scientists have an extremely important role to play in such an education.

MAGE (Denmark)

In view of the past history of industry, as in the case of asbestos where the company doctors knew of asbestosis and mesothelioma in asbestos workers and did not disclose it, do you think that labor unions should put into their contracts that epidemiological studies shall be undertaken and published?

FRIBERG (Sweden)

This might well be a recommendable way. Again, however, both management and labor unions should learn to understand that the publishing of data and the proper execution of epidemiological studies are for the benefit of both parts. Labor unions should also make sure that they have at their disposal highly competent scientists in both epidemiology and toxicology. This is often not the situation at present.

RAMACIOTTI (Switzerland)

Since there is a kind of automatic selection of industrial workers, i.e. the most threatened persons are eliminated, do you not think it dangerous to use results of epidemiological studies carried out in industry to draw up standards for the entire population?

FRIBERG (Sweden)

I agree completely. Due attention must be paid to differences in sensitivity. Workers who for one reason or another have terminated their employment at a given industry should not be omitted in epidemiological studies. They may indeed form the most important subgroup. Moreover, the general population does not consist solely of healthy people and encompasses both age extremes. The exposure time, further, is quite different from what is experienced in industry.

THE CARCINOGENIC RISK FOR MAN OF ENVIRONMENTAL CHEMICALS

L. TOMATIS

International Agency for Research on Cancer, Lyon, France

ABSTRACT

The hypothesis that environmental factors play an essential role in the aetiology of human cancer is receiving wide support and it has been repeatedly asserted that over 80% of human cancers are due to environmental factors.

Environmental factors may act directly on individuals exposed and may affect pregnant women and therefore reveal an effect on a subsequent generation.

A direct effect of environmental factors in producing cancer in man has been shown by: (1) the unequivocal evidence of the chemical origin of occupational cancer, as in the cases of urinary bladder tumours in workers exposed to aromatic amines, lung cancers in workers exposed to bis(chloromethyl)ether, etc.; (2) the well-documented cases of iatrogenic cancers; (3) the positive correlation between cigarette smoking and lung cancer; (4) the different cancer incidences in urban and rural populations and the possible role of air pollution; and (5) the results of studies in migrants showing that for some cancers migrants acquire incidences similar to those of the host countries. Results obtained in experimental carcinogenesis are in keeping with a direct carcinogenic effect of chemicals.

The evidence that exposure of pregnant women to a carcinogen may result in an increased risk of cancer in the progeny has been

provided by the reports on the incidences of vaginal cancer in daughters of women exposed to stilboestrol during pregnancy. The role of prenatal exposure in determining cancer risks in the progeny is fully documented in experimental carcinogenesis.

The possibilities of removing or preventing carcinogenic hazards to man in the environment will be discussed.

It has been stated repeatedly that 80% or more of all human cancers may be attributed to environmental factors. This statement, discussed, but never seriously challenged, has been widely quoted and in practice accepted. This certainly has not made prevention of cancer any easier.

Whilst it seems futile to dispute the real proportion of environmentally-related cancers in the absence of unequivocal evidence, or at least sufficient supporting data, this presentation will be focused on situations in which evidence of the role of environmental factors is well documented. The purpose is to stimulate efforts towards the ultimate goal of our activity, that is, the prevention of cancer. In the case of environmentally-related cancers, prevention can be achieved by the identification and then the removal, or at least substantial decrease, of causative agents. Whilst it seems quite justifiable to concentrate part of our efforts on the search for new environmental hazards, it would be totally unjustified not to operate on hazards for which abundant evidence already exists.

A direct effect of environmental factors in producing cancer in man has been shown by: (1) the unequivocal evidence of the chemical origin of occupational cancer, as in the cases of urinary bladder tumours in workers exposed to aromatic amines, lung cancers in workers exposed to bis(chloromethyl)ether, etc.; (2) the well-documented cases of iatrogenic cancers; (3) the positive correlation between cigarette smoking and lung cancer; (4) the different cancer incidences in urban and rural populations and the possible role of air pollution; and (5) the results of studies on migrants showing that for some cancers migrants acquire incidences similar to those of the host countries. Results obtained in experimental carcinogenesis are in keeping with a direct carcinogenic effect of chemicals.

Evidence that certain types of cancer were related to a particular occupation goes back to the 17th century, when the first observation of a high frequency of lung cancer among workers of a uranium mine were reported. A century later came the observation of Percival Potts on the high incidence of scrotal cancer in chimney sweeps, and a little more than a century later, high incidences of urinary bladder cancer were observed in workers employed in dye factories. Successively, exposure to a number of other organic and inorganic substances, such as asbestos, chromates, nickel, mustard gas, etc. have been shown to result in a high cancer risk.

Two preliminary conclusions can be immediately drawn: (1) the interval between the first observation of a causal relationship of exposure to an environmental factor and cancer, and the adoption of preventive measures is unjustifiably long; and (2) to the majority of chemicals recognized as being human carcinogens, man is exposed because of his occupation.

In relation to the first conclusion, it is perhaps worth mentioning that the carcinogenic risk present in dye factories was first reported in 1896 and confirmed in 1907 (Hueper [1]), but this observation of a carcinogenic effect in man was not judged sufficient and experimental evidence was required. In 1938 Hueper succeeded in inducing urinary bladder cancer in dogs with β-naphthylamine. It was only 20 years later, however, that some measures were taken to prevent massive exposure of workers to β-naphthylamine and this was done only after the masterly work of Case *et al.* [2,3] had again demonstrated beyond any doubt that both naphthylamine and benzidine were carcinogenic to man. In spite of this, there were factories in some countries in which only very recently even elementary measures of precaution were ignored.

As an example of a carcinogenic drug, I would like to mention chlornaphazine, an aromatic amine pertaining to the same chemical group as several other known carcinogens. The fact that an aromatic amine has been used in human therapy, ignoring its chemical parenthood to known human carcinogens, is an indication, among others, of the fragility of the present prevention system and of the limited diffusion given to information on occupational cancer.

Evidence of a carcinogenic effect in man of cigarette smoking has been abundantly demonstrated. The risk of lung cancer in heavy cigarette smokers is high but decreases if exposure to cigarette smoke is discontinued, but still remains higher than in people who have never smoked. According to Doll [4] "the effect of stopping exposure to a carcinogen after a prolonged period of exposure is likely to vary with the nature of the carcinogen". It also depends, for a given carcinogen, on the different target organs, as was the case of the persistence of the risk of developing nasal cancer and the decreasing risk of developing lung cancer

40 years after cessation of exposure to nickel carbonyl (Doll *et al.* [5]).

Cancer incidence varies markedly between urban and rural areas. The differences are perhaps more evident for lung cancer but are certainly not limited to one cancer site. The incidence of colon cancer, for instance, is higher in urban than in rural areas, while rates for stomach cancer show a reverse trend. A higher mortality rate from lung cancer in urban areas than rural areas has been observed in Norway (Kreyberg [6]), in the United States (Carnow and Meier [7], Particulate Polycyclic Organic Matter [8]), and in the UK (Lung Cancer in Western Europe [9]). These differences persist even when rates for smoking habits are standardized. In general, there is a positive correlation between mortality rates for cancer of the lung and population density and urbanization index.

The role of environmental factors in altering cancer risks has received further confirmation from studies on migrants. Assuming that migrants are representative samples of the population in home countries, the differences observed in their cancer experience after their settlement in a host country could be attributed to changes in environmental conditions.

Studies on Japanese migrants to the USA have shown that: (1) mortality from colon cancer, which is rather low in Japan, has undergone a sharp upward shift in Hawaiian born Japanese and to a lesser extent in Japanese migrants in whom the magnitude of the risk was related to the period of residence in the host country (Haenszel and Kurihara [10], Haenszel *et al.* [11]); (2) mortality from stomach cancer, which is very high in Japan, was lower in Japanese migrants and decreased markedly in Japanese born in the USA; and (3) mortality from breast cancer, which is very low in Japan, increased considerably in Japanese born in the USA (Buell [12]). This last observation is based on a study involving a limited number of cases, and contrasts with previous observations indicating the persistence of a low incidence of breast cancer in US-born Japanese. It is worth noting that the apparent persistence of low rates, even after two generations, was taken as a demonstration that for breast cancer, host factors or genetic factors played a preponderant role (Muir [13]). However, Buell's report [12] indicated that environmental factors also play a role on the incidence of breast cancer, which is possibly a good example of an interaction between host genetic and environmental influences.

A comprehensive review of migrant studies published recently (Kmet [14]) lists the factors which may be suspected to cause the change in the cancer experience of migrants. In some instances, and for some types of cancer, the available data indicate that events occurring in adult life may change the cancer risk at a specific site within two decades (Haenszel *et al.* [11]). This is the case for incidence of bowel cancer in Polish migrants to Australia and to the USA (Staszewski and Haenszel [15], Staszewski *et al.* [16]). On the other hand, studies of migrants from the UK to New Zealand (Eastcott [17]) and to South Africa and Australia (Dean [18, 19]) seem to indicate that exposure to pollution early in life may produce persistent effects (Carnow and Meier [7]).

Studies of within-country migration offer good possibilities for evaluating the impact of a changing environment. In a recent study, Cutler and Devesa [20] reviewed studies in cancer incidence and mortality in the USA for white and black populations. Incidence of mortality from cancer of the oesophagus, colon, prostate, lung and pancreas have sharply increased among the black population, and in general the rate of increase has been much higher than in whites for cancer of the lung, pancreas and colon, even though a considerable increase has also been seen in whites. A dramatic increase among blacks was observed for oesophageal cancer, which is on the decrease among whites. Although better medical care may play a limited role, the dramatic upward shift in blacks appears more likely to be attributable to the environmental changes the black population have undergone in the last decades and, in particular, migration from rural areas to the cities, and changes in occupation and in standards of living. Mortality and incidence of stomach cancer have decreased in both whites and blacks, but in the latter at a slower pace than in whites.

Possibility of prevention

One may dispute the real percentage of all cancers related to the environment and, in particular, to chemical agents. What is undisputable, however, is that at present, primary prevention, that is the prevention of exposure to aetiological factors, offers the best perspective for a successful anti-cancer campaign. It also seems the most reasonable approach if one expects to look at cancer as one among others and not the only disease which may be environmentally related. The urban and industrial environments and air pollution are, in fact, not only responsible for an increase in cancer incidence but in the incidence of other chronic diseases, such as chronic bronchitis. Toxic contaminants which may be present in larger quantities in rural than in urban areas are probably responsible for a variety of diseases other than cancer as, for instance, seems to be the case of mycotoxins and aflatoxins in particular (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man [21]). In addition, a number of environmental contaminants may be carcinogenic, mutagenic or teratogenic or they may well have all three characteristics. Efforts towards a primary prevention of cancer can therefore be inscribed within a broad approach towards a healthier, or at least less deadly, environment.

The removal, or at least drastic reduction, in occupational exposure to hazardous chemicals may be obtained in the majority of cases by an improvement in manufacturing procedures. A good example of the success in prevention which can be obtained in this way is the disappearance of the excess risk for nasal sinuses and lung cancers in nickel workers in the UK and Norway who began their work after an industrial process had undergone major changes in order to eliminate exposure of workers to dust and fumes (Doll *et al.* [5], Pedersen *et al.* [22]. The case of recognised chemical carcinogens is, or at least should be, clear, and everybody surely agrees that human exposure to carcinogens must be avoided.

A major problem is the evaluation of the possible carcinogenic effect of a chemical to man in the absence of epidemiological studies or case reports. As there are no objective criteria to extrapolate from experimental data to man, no scientific prediction can be made. Present regulations, however, recommend a zero tolerance in food for chemicals for which experimental evidence of carcinogenicity exists. In so far as food additives are concerned, therefore, an extrapolation for public health purposes is carried out systematically with a procedure which obviously implies that experimental evidence of carcinogenicity is sufficient *per se* to suspect carcinogenicity in man (Tomatis *et al.* [23]). This cautious procedure, with which most people agree, has certainly not been applied to other situations, as for instance, chemicals present in industry and in the general environment.

The validity and limitations of experimental studies in preventing a human hazard could be illustrated by the examples of stilboestrol, bis(chloromethyl)ether, vinyl chloride and DDT. The experimental evidence of the carcinogenicity of stilboestrol existed already in the fifties when stilboestrol was used for human therapy in relatively high doses and was given in particular to pregnant women. It was only at the end of 1970 after the report of an increased risk of vaginal cancer in daughters of women exposed to stilboestrol during pregnancy that some restrictions on its use were introduced. Experimental evidence of the carcinogenicity of bis(chloromethyl)ether existed in 1968 and was confirmed in 1969 but it was only in 1973 after a retrospective epidemiological study showed an excess of lung cancer in workers exposed to bis(chloromethyl)ether that measures to reduce exposure in the working environment were adopted. Similarly, for vinyl chloride, experimental evidence of carcinogenicity existed already in 1970 (Viola [24]) and was long preceded by the evidence of toxic effects of the same type in man and experimental animals. It was only in 1974, however, that measures for drastically reducing its acceptable concentration were adopted and only after a report on the occurrence of a rare type of cancer (angiosarcoma) of the liver among workers exposed to vinyl chloride.

In these three cases a more cautious attitude would have resulted in a successful prevention. We should perhaps not limit our role to that of a sort of necrophore, waiting for a rare type of cancer to appear or for a sufficiently high number of people to be killed by a less rare cancer before being ready to recommend preventive measures.

The case of DDT is particularly complex because: (1) it has already been used for 30 years and not withstanding any measures taken now, it will be in the environment for many years to come; (2) its usefulness in disease control is beyond any doubt: in particular, it has made the malaria campaign a success which has resulted in saving millions of lives; (3) its acute toxicity is relatively low and certainly lower than some of its proposed substitutes. Its chronic toxicity is probably also low, although a number of minor diseases may certainly go undetected; (4) its carcinogenicity was shown and confirmed in the mouse and was limited to the liver. A borderline carcinogenic effect was reported, but not confirmed, in the rat and a lack of carcinogenic effect was reported in the hamster (Tomatis *et al.* [25], Turusov *et al.* [26], Thorpe and Walker [27], Fitzhugh and Nelson [28], Napalkov [29], IARC Annual Report [30], Agthe *et al.* [31]). Measures to restrict and reduce the use of DDT have been taken more because of its impact on the environment at large than because of the experimental evidence of carcinogenicity. DDT is also an example of a chemical for which a risk versus benefit evaluation could be made (Safe Use of Pesticides [32]), with a procedure *a posteriori* which cannot, however, be recommended. In fact, whilst there is no obvious evidence of a carcinogenic effect of DDT in man, it is still not possible at present to exclude it, as no proper epidemiological study on DDT-exposed people has yet been reported.

A risk versus benefit evaluation is currently being made when the use of drugs employed in the therapy of cancer has to be decided. As is well known, most of these drugs are *per se* carcinogenic. Drugs for which experimental evidence of carcinogenicity exists should not be used except for life saving measures and in no case should a decision on its use be made by an individual.

The prevention of lung cancer related to cigarette smoking, although theoretically easier to implement, has encountered serious setbacks and there is no evidence at present that the sale of cigarettes has decreased. There is some indication, however, that the introduction of the filter has contributed to a slight decrease in risk (Wynder *et al.* [33]).

Lung cancer is the greatest cause of cancer deaths in man. Its incidence has considerably increased for at least thirty years and is now showing a strong upward shift in women. This high incidence cannot be explained solely by cigarette smoking and must be, at least partly, related to air pollution. The incidence in urban areas is, in fact, approximately double that observed in rural areas. It has been estimated that a 5% increase in the rate of death from pulmonary cancer can be related to each increment of pollution by one microgram of benzo(a)pyrene per 1000 cubic metres of air (Carnow and Meier [7], Particulate Polycyclic Organic Matter [8]). Conversely, it has been postulated that reduction of air pollution would result in a substantial reduction in lung cancer death rates.

Studies on migrants may offer a clue for the identification of agents involved in the causation of human cancers. The study of Haenszel *et al.* [11] on the incidence of colon cancer in Japanese migrants is an example of the possibility such studies may offer for the identification of possible environmental factors. On the other hand, it must not be forgotten that the environment in its extended meaning includes social status and that evidence exists that certain types of cancer occur with a higher frequency among members of the lower social classes (Clemmesen, Nielsen et al. [34]).

References

1. HUEPER, W.C., "Occupational and environmental cancer of the urinary system", Yale University Press, New Haven and London,(1969).
2. CASE, R.A.M., HOSKER, M.E., McDONALD, D.B., PEARSON, J.T. "Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry", Brit. J. Industr. Med., 11, 75-104 (1954).
3. CASE, R.A.M., HOSKER, M.E., "Tumours of the urinary bladder as an occupational disease in the rubber industry in England and Wales", Brit. J. Prev. Soc. Med., 8, 39-50 (1954).
4. DOLL, R. "Age", in: Host Environment Interactions in the Etiology of Cancer in Man, ed. R.Doll and I.Vodopija, IARC Lyon 1973, pp. 39 - 48.
5. DOLL, R., MORGAN, L.G., SPEIZER, F.E., "Cancers of the lung and nasal sinuses in nickel workers", Brit. J. Cancer, 24, 623-632 (1970).
6. KREYBERG, L., "Aetiology of lung cancer", Universitetsforlaget, Oslo (1969).
7. CARNOW, B.., MEIER, P. "Air pollution and pulmonary cancer", Arch. Environ. Hlth., 27, 207-218 (1973).
8. Particular Polycyclic Organic Matter, National Academy of Sciences, Washington, D.C. (1972).
9. Lung Cancer in Western Europe, Council of Europe, Strasbourg, (1969).
10. HAENSZEL, W., KURIHARA, M., "Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States". J. Natl. Cancer Inst., 40, 43-68 (1968).
11. HAENSZEL, W., BERG, J.W., SEGI, M., KURIHARA, M., LOCKE, F.B., "Large-bowel cancer in Hawaiian Japanese", J. Natl. Cancer Inst., 51, 1765-1779 (1973).
12. BUELL, P., "Changing incidence of breast cancer in Japanese-American women", J. Natl. Cancer Inst., 51, 1479-1483 (1973).
13. MUIR, C.S., "Geographical differences in cancer patterns", in: Host Environment Interactions in the Etiology of Cancer in Man, ed. R.Doll and I. Vodopija, IARC Lyon 1973, pp. 1-13.
14. KMET, J., "The role of migrant population in studies of selected cancer sites: a review", J. Chron. Dis., 23, 305-324 (1970).

15. STASZEWSKI, J., HAENSZEL, W., "Cancer mortality among the Polish-born in the United States. J. Natl. Cancer Inst., 35, 291-297 (1965).

16. STASZEWSKI, J., McCALL, M.G., STENHOUSE N.S., "Cancer mortality in 1962-66 among Polish migrants to Australia", Brit. J. Cancer, 25, 599-610 (1971).

17 EASTCOTT, D.F., "The epidemiology of lung cancer in New Zealand" Lancet, 1, 37-39 (1956).

18. DEAN, G., "Lung cancer among white South Africans", Brit. Med. J., 2, 852-857 (1959).

19. DEAN, G., "Lung cancer in South Africans and British immigrants", Proc. R. Soc. Med., 57, 984-987 (1964).

20. CUTLER, S.J., DEVESA, S.S., "Trends in cancer incidence and mortality in the USA". in: Host Environment Interactions in the Etiology of Cancer in Man, ed. R.Doll and I.Vodopija, IARC Lyon 1973, pp. 15-34.

21. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 1, IARC Lyon (1972).

22. PEDERSEN, E., HØGETVEIT, A.C., ANDERSEN, A., "Cancer of respiratory organs among workers at a nickel refinery in Norway", Int. J. Cancer, 12, 32-41 (1973).

23. TOMATIS, L., PARTENSKY, C., MONTESANO, R., "The predictive value of mouse liver tumour induction in carcinogenicity testing - a literature survey". Int. J. Cancer, 12, 1-20 (1973).

24. VIOLA, P.L., "Cancerogenic effect of vinyl chloride", X Int. Cancer Congress Abstracts, Houston 1970, p.20.

25. TOMATIS, L., TURUSOV, V., TERRACINI, B., DAY, N., BARTHEL, W.F., CHARLES, R.T., COLLINS, G.B., BOIOCCHI, M., "Storage levels of DDT metabolites in mouse tissues following long term exposure to technical DDT", Tumori, 57, 377-396 (1971).

26. TURUSOV, V.S., DAY, N.E., TOMATIS, L., GATI, E., CHARLES, R.T. "Tumors in CF-1 mice exposed for six consecutive generations to DDT", J. Natl. Cancer Inst., 51, 983-997 (1973).

27. THORPE, E., WALKER, A.I., "The toxicology of dieldrin (HEOD). II. Comparative long-term oral toxicity studies in mice with dieldrin, DDT, phenobarbitone, β-BHC and γ-BHC", Food Cosmet. Toxicol., 11, 433-442 (1973).

28. FITZHUGH, O.G., NELSON, A.A., "Chronic oral toxicity of DDT", J. Pharmacol. Exp. Ther., 89, 18-30 (1947).

29. NAPALKOV, N.P. Personal communication.

30. International Agency for Research on Cancer, Annual Report, 1972-1973, Lyon 1973.

31. AGTHE, C., GARCIA, H., SHUBIK, P., TOMATIS, L., WENYON, E., "Study of the potential carcinogenicity of DDT in the Syrian Golden Hamster". Proc. Soc. exp. Biol. (N.Y.), 134, 113-116 (1970).

32. Safe Use of Pesticides, Wld. Hlth. Org. techn. Rep. Ser., No. 513 (1973).

33. WYNDER, E.L., MABUCHI, K., BEATTIE, E.J., "The epidemiology of lung cancer - recent trends", J. Amer. Med. Assoc., 213, 2221-2228 (1970).

34. CLEMMESEN, J., NIELSEN, A., "The social distribution of cancer in Copenhagen, 1943-1947", Brit. J. Cancer, 5, 159-171 (1951).

DISCUSSION

SCHLIPKÖTER (Federal Republic of Germany)

The latent period of malignant tumors is frequently very long. Tumors caused by asbestos, for example, may not appear for 20-30 years Since we cannot wait as long as this, I consider that great importance should be attached to experiments on animals to determine the carcinogenic effects of environmental insults until any chance of carcinogenesis in humans can be excluded. Recent results obtained by our Institute indicate that thin glass fibres are carcinogenic to rats and humans. Should we not therefore pay attention to fibrous dusts of this kind now instead of waiting 20-30 years?

TOMATIS (W.H.O.)

I fully agree with you that more attention should be paid to reliable experimental results and that experimental evidence of a carcinogenic effect of a substance may well predict a similar effect in man. The latency period for cancer in man is often, but not always, as long as 20-30 years. In the survivors of Hiroshima, for instance, it was about 6 years, and in a few cases of urinary bladder cancer following chlornaphazine therapy it was 4-6 years. I was not aware that glass fibres were definitely proved to be carcinogenic to rats and, what is more important, to humans. If this is so, action must be taken immediately to prevent human exposure.

KJELLSTRÖM (Sweden)

The problem of the latency period may be more disastrous than here indicated in the way that when the carcinogenic effect is found in epidemiological studies this is only the start of an increasing trend in the incidence. Even if the exposure is stopped this may occur. In two iron mines in North Sweden the incidence of lung cancer has increased considerably during the last years. The workers are exposed to exhaust gases from diesel engines and radon and this exposure started only some years ago. It will be very important to follow the trends of the lung cancer incidence. Do you know of any data where the incidence has been followed through the years after the initial finding?

Regarding the cost-benefit analysis of profit of chemicals versus the costs of cancer it must be very important to engage the people exposed in the evaluation. The workers in industry must get all the information available about the risks of their exposure and participate in the decision procedure. Is it not the responsibility of scientists to actively take his role of informer and protector of the health of the workers?

TOMATIS (W.H.O.)

You have touched a very important problem. It is often said that occupational cancers represent about 1% of all cancers. I have not found any sound data on which such a statement could be based. What does happen in fact when a chemical is found to be carcinogenic to man? I mentioned in my talk the case of β-naphthylamine and the fight which lasted for more than half a century to prevent exposure to it, but what happens nowadays with other chemicals? It seems to me that following a few papers or case reports referring to the carcinogenic effect of a chemical, very little information is later collected. We do not know, for instance, how many cases of urinary bladder, skin or lung cancer are due to occupational exposure. Some work has been done to follow the trends of urinary bladder cancers due to aromatic amines and of lung and nasal cavity cancer due to exposure to nickel, following initial findings, but there is certainly more to be done in this direction.

I agree with you that a risk-benefit analysis should be done with the participation of the people who run the risk and not only the people who evaluate the benefits. I also agree with you that scientists have a definite responsibility towards society in disseminating information which may be useful in the prevention of cancer.

INTERACTION OF ENVIRONMENTAL CHEMICALS, ENZYMATIC CHANGES AND THEIR POSSIBLE EFFECTS ON HEALTH

HANS L. FALK

National Institute of Environmental Health Sciences, Research Triangle Park, N.C., USA
(temporarily with W.H.O. Geneva)

ABSTRACT

The interactions to be discussed here are responsible for increased or decreased toxicity due to one environmental factor by prior or concommitant exposure to another one. Among the many recorded interactions those were singled out that involve enzyme induction or inhibition, as they may lend themselves to easier interpretation. Nonetheless predictions regarding the effects of such interactions of environmental factors are not as easy as the explanations of the results.

The requirements for enzyme induction throw much light on the complexity of the process. There are differences in this respect between species, strains and individuals and also between organs or tissues of the same species. Chemicals that are lipid soluble often are effective inducers, but other factors are involved too, so that chemicals can be graded from potent to inactive as enzyme inducers. Variations in the increase in certain enzyme activities by different chemicals suggests that multiple enzymes are involved.

Different effects could be produced by chemicals that act as inducers or inhibitors depending on whether the other chemical was toxic but could be deactivated by the induced enzyme or was a precursor of a toxicant and would be activated by the enzyme.

Preceding page blank

Particularly complicated are situations of interactions where multiple enzyme pathways are involved leading to inactive or toxic products as a function of differential enzyme induction.

Although most data came from experiments on laboratory animals enzyme induction is also active in man and has been utilized to good advantage. For many chemicals the effective levels used in laboratory experiments are not much higher than those encountered by man in his daily life.

Several types of interactions have been discussed at a previous session of this symposium and will not be dealt with here, but the emphasis will be on interactions which involve stimulation or inhibition of inducible or non-induced enzyme activity. Although the mechanism of action for many of these situations appears well understood, it is difficult to predict the outcome of these interactions which gives the topic its importance.

Several types of interactions have been discussed at a previous session of this symposium and will not be dealt with here, but the emphasis will be on interactions which involve stimulation or inhibition of inducible or non-induced enzyme activity. Although the mechanism of action for many of these situations appears well understood, it is difficult to predict the outcome of these interactions which gives the topic its importance.

1. Requirements for enzyme induction.

One must start with a discussion of salient features of enzyme induction to appreciate the many modifying factors at work. The capability to respond by enzyme induction is a genetic property possessed by all species that have been studied [1] and where the genes are missing survival is jeopardized. For the perpetuation of the species enzyme induction has played an important role whether we deal with bacteria, insects or mammals. However, the capacity for induction is not the same for all species and varies greatly for species, strains and individuals. Comparing hepatic microsomal activity it can be seen that man is quite low in hydroxylating activity compared to other species. Measured by aminopyrine demethylation, mouse liver was 20 times more efficient, rabbit, guinea pig and rat liver, 10 times, and cat liver, 5 times better than human liver. Cytochrome P_{450} based on mg liver protein was 10 times higher in rodent liver than human, but the P_{450} content could not explain the superior activity of mouse liver compared to other rodent livers [2].

Although enzyme induction in human liver is far less effective than is that of rodents, nonetheless it has recently been utilized in a case of familial unconjugated non-hemolytic jaundice to cure the patient by the administration of 1.5mg/kg DDT for 6 months. It reduced the plasma bilirubin to normal levels where it remained apparently indefinitely, even after DDT was no longer given. His plasma "DDT" level rose from 5 to 1330 ng/ml during treatment and the fat content reached 200 µg/g. After treatment plasma "DDT" levels declined slowly [3].

Effective reduction of "DDT" storage was observed in patients on long-term anticonvulsant treatment. In patients on phenytoin or phenytoin and phenobarbital the blood DDE level was less than 2ppb, compared to a mean of 4.5 ppb in controls and the level in fat was 0 compared to a mean of 5.5 ppm in controls. Phenobarbital alone was less effective [4].

There are many variables which cause differences in enzyme induction. It may depend on the sex and age of the animal. Newborn animals are quite low in microsomal enzyme activity, but the young rat can respond with a 10-fold increase in induction compared to a 2-fold increase in the adult rat [5]. It also depends on the nutritional status of the animal, on the nature of the inducer and the type of enzyme activity measured as will be discussed below.

Inducers are lipid-soluble and non-toxic for the tissue in which they must accumulate to a certain level for enzyme induction. The compound administered need not be the inducer, but a metabolite of the compound may be effective, such as DDE. Those chemicals that remain hydrophobic and are stored in specific organs will be far better inducers than more hydrophilic ones or those that can be readily metabolized and conjugated for rapid elimination, but even such compounds like ethanol may act as inducers if the concentration is high.

Elimination of the compound may, however, not always complete the story. Enzymes of microbial origin may hydrolyze the conjugates or, by enzyme induction, cause the formation of different products which on reabsorption may show enzyme induction or, even worse, may exert a toxic effect. A case in point is the enzyme induction in fecal bacteria of rats exposed to cyclamate, which led to increased absorption of cyclohexylamine. The ability to convert cyclamate to cyclohexylamine was readily lost when cyclamate was no longer fed to the animals [6].

Although most studies on enzyme induction have focused on hepatic microsomes, it should be mentioned that certain inducible enzymes like glucuronyl transferase may be associated only partly with the microsome fraction.

Other tissues and organs are capable of enzyme induction. It was demonstrated for the lung, adrenal and mammary gland of rats, [7] rat and rabbit kidney [8], and the skin of mice, [9]. Aryl hydroxylase activity was demonstrated for the duodenal mucosa of laboratory animals and man [10]. In comparative studies on isolated perfused rabbit liver and lung preparations enzyme induction of p-hydroxylation of N-methylaniline by phenobarbital was studied. The lung was half as active as the liver, but based on organ weight the lung was more active than the liver [8]. Comparing enzyme induction in liver and kidney of the rabbit by phenobarbital, liver was found to have the higher rate for ring hydroxylation and N-dealkylation of N-methylaniline than had the kidney. Other tissues examined in this study were barely active. The increased enzyme activity was correlatable with increases in yields of microsomes in liver and kidney and an increased liver weight [8]. It should be noted that N-hydroxylation of N-methylaniline was not affected by enzyme induction, an important observation since this step often leads to toxic products.

A few inducible enzymes have already been mentioned, but the list should contain N-, O-, and S-oxidative demethylases, o- and p-aromatic ring hydroxylases, N-hydroxylase, azo reductase, omega-oxidase and glucuronide transferase to mention the most important [11].

Conditions for maximal enzyme induction may not always be encountered. In the absence of inducers microsomal hydroxylating enzyme activity was at very low levels when a protein-free diet was fed to rats, i.e. it was 1/7 the level on a normal diet. In the presence of an inducer, DDT, but still on the protein-free diet the activity could be stimulated to reach near normal levels, but DDT and a normal diet produced the expected large increase in enzyme activity [12].

On raising the protein content to 3%, i.e. still a low protein diet, the induced enzyme activity rose to 33% of normal as did cytochrome P_{450}. On 6% protein in the diet the induced enzyme activity was 50% of normal giving a good indication for dietary protein requirements for adequate enzyme induction. On the protein free diet, rats showed reduced hepatic N-demethylase activity, but increased N-oxidation of dimethylaniline [13]. On a low choline diet low enzyme induction was observed, suggesting the need for choline as a component of the phospholipid structure of the enzyme complex.

Riboflavin is also a required component for effective microsomal enzyme activity. Azo reductase is a flavoprotein which was instrumental in the 1940s to give early clues to investigators of carcinogenesis on factors that would protect animals against carcinogenic azo dyes on the basis of dietary supplements [14,15]. Similarly, on a vitamin E deficient diet N-demethylation was significantly reduced while N-oxygenated products were increased. The addition of 2 mg vitamin E/g diet for 4 days increased N-demethylation and reduced N-hydroxylation of N-dimethylaniline [16].

These bits of information fit together to describe the requirements for effective enzyme induction if the inducer reaches the required level. The process requires DNA-dependent RNA synthesis and protein synthesis. One of the first enzymes synthesized is delta-aminolevulinic acid synthetase which is required for cytochrome P_{450} synthesis. These proteins are rapidly increased, but their half life is very short. On induction RNAase activities are inhibited so that more enzyme can be synthesized. By the use of puromycin it could be shown that some of the induced enzyme activity was not the result of de novo synthesis but may result from activation of enzyme precursors [17,18].

Some chemicals which act as enzyme inducers have already been mentioned. Of the various classes of chemicals, the polycyclic aromatic hydrocarbons (PAH) have been studied in detail. Not all were equally effective. Using rat liver homogenate and measuring certain polar 7, 12-dimethylbenz(a) anthracene (DMBA) metabolites [19] and determing 8-hydroxybenzo(a)pyrene formation in rat placenta, comparisons of a number of PAH as enzyme inducers are possible [20]. 20-Methylcholanthrene (MC) and benz(a)anthracene (BA) were most effective. Benzo(a)pyrene and (BaP) and chrysene were also quite effective in both systems, while anthracene and fluoranthene were weak. Pyrene, perylene, phenanthrene, fluorene and naphthalene required large doses for a weak response or were entirely inactive. [21].

Organochlorine insecticides have been tested and were generally found to be very effective inducers [22,23] Chlordane, methoxychlor, DDT, DDE, DDD, endrin, aldrin, dieldrin, hexachlorocyclohexanes, heptachlor and its epoxide were all active. Chlordane and DDT were each given to rats twice daily(25mg/kg)for 10 days and their liver microsomes were incubated with testosterone, estradiol-17beta, progesterone or desoxycorticosterone (700 mμmoles) in the presence of a TPNH-generating system [24]. Metabolism of these steroid hormones to more polar products was greatly enhanced, an effect which has been considered the cause of the poor survival of some species of birds of prey.

Steroid hormones on their part cause hepatic microsomal enzyme induction. Progesterone has been studied in particular and was found to give rise to a 5beta metabolite, which caused increased hepatic smooth endoplasmic reticulum, delta-aminolevulinic acid synthetase and cytochrome P_{450} activity. It was thought capable of aggravating conditions of porphyria. This compound is also present in human milk and by inhibiting glucuronyl transferase appears to be responsible for prolonged unconjugated hyperbilirubinemia in neonates during breast feeding [25].

The extent to which synthetic progestogens can act as enzyme inducers and as competitive inhibitors of these enzymes is in need of study.

Not mentioned so far as potent enzyme inducers, because they do not belong into the picture of environmental pollutants, have been the pharmaceutical agents, particularly analgesics, hypnotics, hypoglycemics, antihistamines, anticonvulsants and anti-inflammatory drugs [26].

The observation that cigarette smoking increased the BaP hydroxylase and 3'-methyl-4-monomethylaminoazobenzene N-demethylase activity of human placentas is of great interest. In non-smokers no such activity was detected. There was, however, considerable variation in the activity of the 2 enzymes which could not be explained by the extent of smoking. Aromatic polycyclic hydrocarbons were suggested as responsible for the induction [20]. Nicotine, however, is more likely to be the inducer when considering quantitative requirements. That nicotine is indeed a good inducer could be shown on mice given orally 2.28 mg/kg/ day of nicotine and measuring the ataxia produced by i.p. injection of 200 mg/kg meprobamate. The period of ataxia was significantly decreased on nicotine treatment. When nicotine administration was stopped the duration of ataxia returned to normal levels in 4 days. In vitro studies confirmed the faster metabolic degradation by mouse liver of meprobamate in animals treated for 2 days with nicotine. Ethionine prevented the increase [27]. These observations are of great interest because of the widespread intake of nicotine which belongs to a class of compounds, the alkaloids, which have not been considered to be effective enzyme inducers.

Chemicals belonging to other classes have been studied sporadically as enzyme inducers. Among them are dietary components, present as anutrients, food additives or residues. Obtaining data on enzyme inducers of that type is difficult as a semi-synthetic diet is inadequate as baseline for enzyme induction. However, a number of flavones were shown to induce BaP hydroxylase activity in rat liver and lung, including tangeretin and nobiletin besides flavone itself[28]. Safrole was shown to induce biphenyl hydroxylase, nitro reductase, glucuronyl transferase and cytochrome P_{450} in rat liver [29]. It is of interest to note that safrole and many related methylenedioxyphenyl derivatives are effective inhibitors of microsomal oxidative enzymes, but become capable inducers after they have been metabolized. Among the pesticides, besides the organochlorine insecticides, the urea herbicides were shown to be active inducers. The most effective ones were diuron and herban causing increased O-demethylase activity and EPN (O-p-nitrophenyl phenylphosphonothioate) detoxification in rat liver when 10-300 mg/kg/day had been administered for 5 days [30].

Among the food additives butylated hydroxytoluene (BHT) is of importance. When fed to rats above the level of 0.1% in the diet the liver enlargement paralleling the stimulation of microsomal enzyme systems was not considered physiological but a toxicologic effect. On day 2 of BHT feeding, enzyme activity was already enhanced and continued rising as feeding was continued. The level of BHT in fat stabilized at 100 ppm in that study. BHA (butylated hydroxyanisole) was a less effective enzyme inducer, but also caused liver enlargement in rats [31]. Both chemicals have been shown to be radiosensitizers in drosophila melanogaster and murine leukemia and lymphoma cells, causing 1.6 times as many sex-linked recessive lethal mutations in fruitflies on exposure to 1.2 Krad gamma-radiation as did radiation alone. The mechanism of this symergism has not been clarified [32].

2. Interactions involving enzyme induction.

The variables affecting microsomal enzyme induction discussed above will enable us to understand the interactions involving enzyme induction that much better. Thus feeding rats a low protein diet reduced the hepatic microsomal hydroxylase activity and dramatically reduced carbon tetrachloride toxicity. The LD_{50} of CCl_4 was reached only at 14.7 ml/kg on the protein-free diet compared to 6.4 ml on a normal diet. When the rats were pretreated with phenobarbital the LD_{50} was reached at 0.5 ml/kg. Microsomal enzymes are responsible for forming a CCl_3 free radical, the toxic metabolite [12,33].

Rats on a protein-free diet were also more resistant to the lethal effects of dimethylnitrosamine (DMN). The LD_{50} was at 79 mg/kg on the protein deficient diet compared to the 45 mg/kg on the regular diet. Hepatic microsomal enzyme activity dropped considerably in 4 days on the protein deficiency, reflected in very low metabolism of DMN. The metabolism of DMN by kidney slices, however, was not affected. When a large dose of DMN (60 mg/kg) was given to rats i.p. while kept on this protein-free diet no liver tumors were found, but kidney tumors developed in all animals in 8 to 12 months [34]. Similarly, the mutagenic activity of nitrosamines was shown to depend on the level of protein in the diet. On a protein-free diet the mutagenicity of DMN for Salmonella typhimurium in the host-mediated assay was decreased, while that of N-methyl-N-nitrosourea which requires no metabolic activation was increased. In mice on a pure casein diet the opposite effects were observed with these nitrosamines, which were explained on the basis of dietary modification of hepatic microsomal enzyme activity, essential for activation of DMN and effective in the detoxification of N-methyl-N-nitrosourea [35].

Rats fed 4-dimethylaminoazobenzene (DAB) had far fewer liver tumors when the diet was supplemented with 200 μg riboflavin and 2 g casein. This supplement protected rats also against other carcinogenic azo dyes. The discovery of an hepatic microsomal enzyme that cleaved DAB into aniline and dimethyl aniline - a flavoprotein - helped to explain the findings. Azo reductase activity could be increased by incubating liver slices with riboflavin [36].

The carcinogenic response to MC could be halved if the mice were fed a diet containing wheatgerm oil [37]. Feeding 30 - 100 times the dietary requirement for alpha-tocopheol to C57 leaden mice produced only half as many sarcomas as were seen in animals on a normal diet given the same s.c. dose of MC in mineral oil [38].

Several studies showed alterations in tumor incidence resulting from interactions for which enzyme induction and enhanced detoxification was the most likely explanation. Simultaneous feeding to rats of 3'-methyl-4-dimethyl-aminoazobenzene and MC produced a far lower incidence of hepatomas and bileduct carcinomas than feeding the azo dye alone [39]. In further studies the temporal relationship of feeding the 2 compounds was of significance. When MC was added to the azo dye diet in the first 6 weeks hepatoma formation was prevented. When MC was added from the 6th to 10th week it was only partly successful in its protection. However, adding the hydrocarbon only after 10 weeks of azo dye feeding was non-protective. The temporal increase in hepatic N-demethylase activity in the MC-fed animals which can inactivate the carcinogen could explain the findings [40]. With DAB and barbital the reduced hepatoma incidence was similarly explained on the basis of enhanced enzyme induction [41].

Using fluorenyl acetamide (FAA) as precursor of a liver carcinogen and MC as inducer reduced the incidence of mammary tumors, hepatomas and earduct tumors in rats indicating that the precursor was metabolized preferentially by aromatic ring hydroxylation instead of by N-hydroxylation, thus producing inactive compounds instead of the proximate carcinogen [21].

However, an explanation of the results of feeding rats N,N'-(2,7-fluorenylene)-bisacetamide with DMBA as enzyme inducer and carcinogen is more difficult to give. The DMBA was placed into an artificial diverticulum in the glandular stomach where it produced few tumors on its own. The aromatic amine alone produced hepatomas, cholangiofibrosis, earduct tumors and intestinal cancers. These pathological conditions were markedly reduced when both chemicals were administered, but instead, a high incidence of forestomach papillomas, basal cell carcinomas, squamous cell carcinomas, carcinomas of the glandular stomach as well as mammary, uterine and skin cancers were observed [42]. Explaining these findings may be possible but predicting them is another matter.

Interactions of these types have also been reported in the area of teratology. Thalidomide (150 mg/kg) given to rabbits from day 7 to 12 of gestation produced no malformations in the offsprings unless on day 6 60mg/kg of CCl_4 was administered orally. Evidence of liver damage was seen in the maternal animals [43].

Other chemicals that can alter maternal hepatic microsomal enzyme activity can affect the incidence of malformations in the fetuses as was shown for phenobarbital (50 or 100 mg/kg) given to mice from day 8 to 10 of gestation and the teratogenic cyclophosphamide (20 mg/kg) given on day 10 only. Malformations, as seen with cyclophosphamide alone were nearly completely abolished except for the incidence of open eyes and polydactyly which persisted [44].

3. Interactions involving enzyme inhibition.

The second part of the experiment discussed above described the doubling of the incidence of malformations due to cyclophosphamide by giving an enzyme inhibitor, i.e. beta-diethylaminoethyl diphenylpropylacetate (SKF-525A) (32 mg/kg) to pregnant mice from day 8 to 10.

Inhibition of microsomal enzyme activity can occur at the normal level as well as in the induced state. In comparison to enzyme induction which may last for several weeks following a single administration of an inducer, enzyme inhibition is comparatively short lived and reversible.

Pesticide synergists which found widespread use as a household insecticide combine piperonyl butoxide or a related compound with a pyrethrum insecticide. They produce their lethal effect at 1/10 the normal dose of insecticide. They function by temporarily inhibiting detoxifying enzyme systems in insects. They also prevent enzymatic dehydrochlorination of DDT in soil organisms, epoxidation of aldrin or heptachlor and ring hydroxylation of polycyclic hydrocarbons in mammals, etc. Their activity as detoxification inhibitors could be considered a potential health hazard for man were it not for the limited production of these pesticide synergists because of sparce supplies of the starting material and the interesting fact that these compounds on being metabolized themselves give rise to enzyme inducers.

However it should be mentioned again that methylenedioxyphenyl derivatives are also present as anutrients in sesame oil, sasafras oil, etc [45].

Ozone was found to be a good BaP hydroxylase inhibitor whether the enzyme was in the normal or induced state. Significant inhibition was observed when hamsters were exposed for 3 hours to 0.75, 3 or 10 ppm ozone and sacrificed 30 minutes later. There was no effect on hepatic microsomal enzyme activity [46].

Another air pollutant, carbon monoxide, is a potent inhibitor of microsomal enzymes as it will bind to cytochrome P_{450} inhibiting its function. Inhibition of the metabolism of azo dyes, drugs and steroid hormones depend on the ratio of CO to O_2 and it was noted that the ratio of CO to O_2 for 50% inhibition of hydroxylation of testosterone was different dependent on which position in the molecule was hydroxylated. It was 0.93, 1.54 and 2.36 for 16alpha-, 6beta-, and 7alpha-hydroxylation of testosterone [47].

Inhibition of the metabolism of estradiol-17beta and estrone in immature female rats by CCl_4 has been reported. In vitro metabolism of estrone was 70% inhibited by 0.06 mg/kg CCl_4. In in vivo studies CCl_4 interfered with estrogen metabolism, potentiated the uterotropic action of the compounds and increased the concentration of the estrogens in the uterus. Tetrachloroethylene by contrast produced none of these effects [48]. In other studies CCl_4 administered to rats increased the sleeping time evoked by hexobarbital, reduced the in vitro metabolism of hexobarbital, impaired the oxidation of aminopyrine and the reduction of p-nitrobenzoic acid. The activity was reduced to 10% of normal within 8 hours following administration and remained at that level for 24 hours after administration of CCl_4. In contrast chloroform had little effect and methylene chloride was ineffective as an inhibitor [49].

The skin tumor incidence due to ethyl carbamate could be reduced to only 10% by the administration of an equimolar amount of butyl carbamate to mice. [50]. The explanation was given that the urethane activating enzyme could be inhibited by a structural analog.[51]. Similarly a toxic dose of FAA (0.03%) could be safely administered in the diet to rats if acetanilide at a level of 0.8% was also given. No hepatomas were seen, only some hepatic hyperplasia. Halving the dose of acetanilide increased only the degree of hyperplasia, but produced no hepatomas. Since FAA requires metabolic activation to become a hepatocarcinogen acetanilide apparently pre-empts N-hydroxylation of FAA by being itself preferentially metabolized [52].

A 50-fold potentiation of toxicity of malathion by another organophosphorus insecticide (EPN) was reported in 1957. A metabolite of EPN was found to possess greater affinity for aliesterases than cholinesterase and inhibition of the aliesterase prevented normal detoxification of malathion thus leading to the enhanced toxicity. This effect however is only realized at high dose levels when the enzyme systems become overloaded. [53].

Not quite the same results were obtained with Delnav^R, another organophosphorus insecticide preparation consisting of isomers of 2,3-p-dioxanedithiol-S,S-bis-(0,0-diethyl phosphorodithioate) which would only show additive toxicity when simultaneously administered with malathion. However, if administered 4 days prior to malathion to rats it would enhance the expected toxicity considerably [54].

EPN not only enhanced the toxicity of malathion, but that of dimethoate by blocking amidase activity as could be shown in mice and guinea pigs. Houseflies metabolize organophosphorus insecticides preferentially by means of phosphatase. Therefore inhibition of metabolism of malathion or dimethoate by these compounds does not occur to any extent and the synergism is not observed in houseflies [55].

As a last example I should mention the deliberate use of monamine oxidase (MAO) inhibitors which have found widespread use, but were responsible for many cases of paroxysmal hypertensive attacks. Most of the patients on specific MAO inhibitors had eaten unknowingly high doses of certain amines with their food, particularly tyramine, which is present in large quantities in herring, cheeses like Cheddar or Gruyère, but also in yeast, beer, wine, etc. This toxicity can also be elicited from other amines which cannot be detoxified in persons on MAO inhibitor drugs [56].

The interactions discussed here have produced 10 to 50 fold aggravation or amelioration of toxicity and should help all of us concerned with environmental pollution problems to keep such interactions in mind when considering potential health hazards from individual pollutants alone, even though they occur in a milieu of multiple exposures to many environmental chemicals.

BIBLIOGRAPHY

1. Gielen, J.E., Goujon, F.M. and Nebert, D.W., "Genetic regulation of aryl hydrocarbon hydroxylase induction. Simple Mendelian expression in mouse tissues in vivo". J.Biol. Chem. 247: 1125 (1972).

2. Remmer, H. "Induction of drug metabolising enzymes in different animal species", in"The problems of species difference and statistics in toxicology", Proc. Europ. Soc. Study Drug/Toxicity, Volume 11, 14 (1970).

3. Thompson, R.P.H., et al. "Treatment of unconjugated jaundice with dicophane". Lancet 2, 4 (1969).

4. Davies, J.E., Edmundson, W.F., Carter, C.H., and Barquet, A. "Effect of anticonvulsant drugs on dicophane (D.D.T.) residues in man". Lancet 2, 7 (1969).

5. Cramer, J.W., Miller, J.A., and Miller, E.C., "The hydroxylation of the carcinogen 2-acetylaminofluorene by rat liver; Stimulation by pretreatment in vivo with 3-methylcholanthrene". J.Biol.Chem. 235, 250 (1960).

6. Scheline, R.R., "Toxicological implications of drug metabolism by intestinal bacteria", in "Toxicological problems of drug combinations", Proc. Europ. Soc. Study Drug Toxicity, Volume 13, 35 (1972).

7. Huggins, C., and Fukunishi, R., "Induced protection of adrenal cortex against 7,12-dimethylbenz(a)anthracene". J. exp. Med., 119, 923 (1964).

8. Uehleke, H., "Extrahepatic microsomal drug metabolism" in "Sensitization to drugs", Proc. Europ. Soc. Study Drug Toxicity Volume 10, 94 (1969).

9. Wattenberg, L.W., "Morphologic histochemical studies of the benzpyrene hydroxylase system". Prox. Amer. Assoc. Cancer Res., 3, 370 (1962).

10. Wattenberg, L.W., Leong, J.L., and Strand, P.J. "Benzpyrene hydroxylase activity in the gastrointestinal tract". Cancer Res. 22, 1120 (1962).

11. Gelboin, H.V., "Carcinogens, enzyme induction and gene action". Adv. Cancer Res. 10, 1 (1967).

12. Judah, J.D., McLean, A.E.M. and McLean, E.K., "Biochemical mechanisms of liver injury". Am. J. Med. 49, 609 (1970).

13. McLean, A.E.M. and McLean, E.K., "The effect of diet and 1,1,1-trichloro-2,2-bis-(p-chlorophenyl)ethane (DDT) on microsomal hydroxylating enzymes and on sensitivity of rats to carbon tetrachloride poisoning". Biochem. J. 100, 564 (1966).

14. Kensler, C.J. "The influence of diet on the riboflavin content and the ability of rat-liver slices to destroy the carcinogen N,N-dimethyl-p-aminoazobenzene". J.Biol. Chem. 179, 1079 (1949).

15. Mueller, G.C. and Miller, J.A., "The reductive cleavage of 4-dimethylaminoazobenzene by rat liver. The intracellular distribution of the enzyme system and its requirements of triphosphopyridine nucleotide". J.Biol. Chem. 180, 1125 (1949).

16. Arrhenius, E., "Effects on hepatic microsomal N- and C-oxygenation of aromatic amines by in vivo corticosteroids or aminofluorene treatment, diet, or stress". Cancer Res. 28, 264 (1968).

17. Remmer, H. "The induction of the microsomal oxidase (cyt.P.450)", in "Toxicological problems of drug combinations", Proc. Europ. Soc. Study Drug Toxicity 13, 10 (1972).

18. Seifert, J., Vacha, J., and Remmer, H., "Phenobarbital and liver growth, A biochemical study" in "The correlation of adverse effects in man with observations in animals", Proc. Europ. Soc. Study Drug Toxicity, 12, 253 (1971).

19. Levin, W. and Conney, A.H., "Stimulatory effect of polycyclic hydrocarbons and aromatic azo derivatives on the metabolism of 7,12-dimethylbenz(a)anthracene". Cancer Res. 27, 1931 (1967).

20. Welch, R.M. et al., "Stimulatory effect of cigarette smoking on the hydroxylation of 3,4-benzpyrene and the N-demethylation of 3'-methyl-4-monomethylaminoazobenzene by enzymes in human placenta". Clin. Pharmacol. & Therap. 10, 100 (1969).

21. Miller, E.C. et al. "On the protective action of certain polycyclic aromatic hydrocarbons against carcinogenesis by amino azo dyes and 2-acetylaminofluorene". Cancer Res. 18, 469 (1958).

22. Fouts, J.R. "Factors influencing the metabolism of drugs in liver microsomes". Ann. New York Acad. Sc. 104, 875 (1963).

23. Hart, L.G. and Fouts, J.R. "Further studies on the stimulation of hepatic microsomal drug metabolizing enzymes by DDT and its analogs". Arch. exper. Path. u. Pharmakol. 249, 486 (1965).

24. Conney, A.H. et al. "Effects of pesticides on drug and steroid metabolism". Clin. Pharmacol & therap. 8, 2 (1967).

25. Adlercreutz, H. and Tenhunen, R. "Some aspects of the interaction between natural and synthetic female sex hormones and the liver". Am.J.Med.49, 630 (1970).

26. Conney, A.H. "Implications of drug induced changes in microsomal enzymes to toxicity of drugs; in Drugs and Enzymes, volume 4, pp 277-296 (Macmillan New York) (1965)

27. Wenzel, D.G. and Broadie, L.L. "Stimulatory effect of nicotine on the metabolism of meprobamate". Toxicol & Appl. Pharmacol. 8, 455 (1966).

28. Wattenberg, L.W., Page, M.A. and Leong, J.L. "Induction of increased benzpyrene hydroxylase activity by flavones and related compounds". Cancer Res. 28, 934 (1968).

29. Parke, D.V. and Rahman, H. "The induction of hepatic microsomal enzymes by safrole". Biochem. J. 119, 53 (1970).

30. Kinoshita, F.K. and DuBois, K.P. "Induction of hepatic microsomal enzymes by Herban R, Diuron, and other substituted urea herbicides". Toxicol & Appl. Pharmacol. 17, 406 (1970).

31. Gilbert, D. and Golberg, L. "Liver response tests.III. Liver enlargement and stimulation of microsomal processing enzyme activity". Fd. Cosmet. Toxicol 3, 417 (1965).

32. Prasad, O.M. and Kamra, O.P. "Radiosensitizing property of butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) in drosophila melanogaster". First International Conference on Environmental Mutagens, Pacific Grove, Calif., USA, p 19 (1973).

33. Slater, T.F. "Necrogenic action of carbon tetrachloride in the rat. A speculative mechanism based on activation". Nature 209, 36 (1966).

34. Swann, P.F. and McLean, A.E.M. "The effect of diet on the toxic and carcinogenic action of dimethylnitrosamine". Biochem.J. 107, 14 (1968).

35. Zeiger, E. "Dietary effects on the mutagenicity of N-nitroso compounds in the host mediated assay". First International Conference on Environmental Mutagens, Pacific Grove, Calif., USA, p 15 (1973).

36. Kensler, C.J. et al. "Partial protection of rats by riboflavin with casein against liver cancer caused by dimethylaminoazobenezene". Science 93, 308 (1941).

37. Jaffe, W.G. "The influence of wheat germ oil on the production of tumors in rats by methylcholanthrene". Exp. Med. Surg. 4, 278 (1946).

38. Haber, L. and Wissler, R.W. "Effect of vitamin E on carcinogenicity of methylcholanthrene". Proc. Soc. exp. Biol. 111, 774 (1962).

39. Richardson, H.L., Stier, A.R. and Borsos-Nachtnebel, E. "Liver tumor inhibition and adrenal histological responses in rats to which 3'-methyl-4-dimethylaminoazobenzene and 20-methylcholanthrene were simultaneously administered". Cancer Res. 12, 356 (1952).

40. Meechan, R.A., McCafferty, D.E. and Jones, R.S. "3-Methylcholanthrene as an inhibitor of hepatic cancer induced by 3'-methyl-4-dimethylaminoazobenzene in the diet of the rat. A determination of the time relationship". Cancer Res. 13, 802 (1953).

41. Ishidate, M., Wattanabe, M. and Odashima, S. "Effect of barbital on carcinogenic action and metabolism of 4-dimethylaminoazobenzene". Gann 58, 267 (1967).

42. Odashima, S. "Combined effect of carcinogens with different action. IV. Effect of 7,12-dimethylbenz(a)anthracene placed in an artificial diverticulum of the glandular stomach combined with feeding of N,N'-(2,7-fluorenylene)-bisacetamide to rats". Gann 2, 81 (1968).

43. Heine, W. et al. "Thalidomid-Embryopathie bei Kaninchen nach passagerer Leberschädigung der Muttertiere durch Tetrachlorkohlenstoff". Klin. Wschr. 42, 592 (1964).

44. Gibson, J.A. and Becker, B.A. "Effects of phenobarbital and SKF 525-A on the teratogenicity of cyclophosphamide in mice". Teratol. 1, 393 (1968).

45. Falk, H.L. and Kotin, P. "Pesticide synergists and their metabolites: Potential hazards". Ann.New York Acad. Sc. 160, 299 (1969).

46. Palmer, M.S., Swanson, D.H. and Coffin, D.L. "Effect of ozone on benzpyrene hydroxylase activity in the Syrian golden hamster". Cancer Res. 31, 730 (1971).

47. Conney, A.H. et al. "Inhibitory effect of carbon monoxide on the hydroxylation of testosterone by rat liver microsomes". J.Biol. Chem. 243, 2912 (1968).

48. Levin, W., Welch, R.M. and Conney, A.H. "Effect of carbon tetrachloride and other inhibitors of drug metabolism on the metabolism and action of estradiol-17beta and estrone in the rat". J.pharmacol & exper. therap. 173, 247 (1970).

49. Dingell, J.V. and Heimberg, M. "The effects of aliphatic halogenated hydrocarbons on hepatic drug metabolism". Biochem. Pharmacol. 17, 1269 (1968).

50. Garcia, H. "Inhibition of tumorigenic action of urethane by butyl carbamate". Biologica 34, 11 (1963).

51. Kaye, A.M. "A study of the relationship between the rate of ethyl carbamate (urethan) catabolism and urethan carcinogenesis". Cancer Res. 20, 237 (1960).

52. Yamamoto, R.S. et al. "Inhibition of the toxicity and carcinogenicity of N-2-fluorenylacetamide by acetanilide". Toxicol. appl. Pharmacol 13, 108. (1968).

53. Frawley, J.P. et al. "Marked potentiation in mammalian toxicity from simultaneous administration of two anticholinesterase compounds". J. Pharmacol & exper. therap. 121, 96 (1957).

54. Frawley, J.P. et al. "Toxicologic investigations on Delnav^{R}". Toxicol. appl. Pharmacol. 5, 605 (1963).

55. Uchida, T., Zschintzsch, J. and O'Brien, R.D. "Relation between synergism and metabolism of Dimethoate in mammals and insects". Toxicol. appl. Pharmacol. 8, 259 (1964).

56. Lévy, J. and Michel-Ber, E. "Difficulties and complications caused in man by monoamine oxidase (MAO) inhibitors, with special reference to their specific and secondary pharmacological effects", in "Toxicity and side-effects of psychotropic drugs", Proc. Europ. Soc. Study Drug Toxicity, 9, 223 (1968).

DISCUSSION

ZIELHUIS (Netherlands)

Should one take into account enzyme induction or inhibition in setting acceptable daily intakes (ADT) for food additives or in setting permissible limits for occupational and ambient exposure? Should enzyme induction or inhibition at relevant dosage range be regarded as inacceptable?.

FALK (W.H.O.)

At this stage we are not adequately equipped to make meaningful recommendations. In rodents the level of dietary intake of inducers has not been adequately documented. The lowest level of 2-3 week feeding of DDT resulting in barely detectable enzyme induction was 1 ppm (1), 2.5 ppm (2) and 3.3 ppm (3). For lindane as inducer the dietary feeding level was 0.5 ppm at which induction could already be observed (4). For most other compounds, we do not have such data, which are needed to be able to evaluate the total picture, i.e. for the human we need to know the level of inducer in the diet and its relative potency. With this information in hand, ADIs could be set, but one would have to determine their signigicance if most people are reasonably weakly "induction-responsive".

On the other hand, attention should be paid to workers exposed to high doses of inducers and patients on treatment with drugs which are potent inducers.

References

1. Kinoshita, F. K. et al
Quantitative measurement of induction of hepatic microsomal enzymes by various dietary levels of DDT and toxaphene in rats.Toxicol & Appl. Pharmacol. 9, 505-513, 1966.

2. Gillett J. W.
"No-effect" level of DDT in induction of microsomal epoxidation J. Agr. Food. Chem., 16, 295-7, 1968

3. Hoffman, D. G. et al
Stimulation of hepatic drug-metabolizing enzymes by chlorophenothane (DDT); the relationship to liver enlargement and hepato-toxicity in the rat. Toxicol. & Appl. Pharmacol., 16, 171-8, 1970.

4. Kolmodin-Hedman, B. et al.
Effect of exposure to lindane on drug metabolism: decreased hexobarbital sleeping time and increased antipyrine disappearance rate in rats. Toxicol. & Appl. Pharmacol., 20, 299-307, 1971.

SANOTSKY (USSR)

What are the criteria for differentation between harmful and not harmful changes of enzyme activity in relation to the general state of health?

FALK (W.H.O.)

Changes accompanying hepatic enzyme induction are usually reversible and therefore considered of a physiological and, by itself, harmless nature. In the state of hyperplasia, the liver may be prone to toxic action by other environmental chemicals. I mentioned CCl_4 as an example.

When the enzyme-inducer produces hyperplastic changes which do not regress, a state of damage may be considered permanent which could be expected in rodents, at least, to lead to abnormal nodule formation.

Whether enzyme induction, even only of a transitory nature, is beneficial or harmful, will depend on the other chemicals encountered by the organism which may be detoxified or transformed to a more toxic agent.

PHILP (U.K.)

Dr. Falk referred to the use of semi-synthetic diets in testing of food additives.

This type of diet is extremely useful in such tests and is preferrable for better control of the ingrediants. What was the basis for his comment in his paper that "a semi-synthetic diet is inadequate as a base line for enzymatic production" suggesting that enzyme induction would be difficult to detect if such a diet was used.

FALK (W.H.O.)

In studies of interactions which are long term studies in the majority of cases a completely synthetic diet has never been used, because of the great expense. When these interaction studies used well monitored diets they would not get information on all enzyme inducers present as addition, contaminants or anentriant food components.

Oftentimes little attention was paid to that matter in the past, since enzyme induction was not taken into consideration.

On enzyme induction studies a semisynthetic diet may also present problems if the various oils are not adequately identified and studied for contaminant, antioxidants and other components.

OLOFFS (Canada)

Dr. Falk, you said that the degree of enzyme induction in humans is quite variable, and has been reported to range from 130% (of normal) to as high as 450%. Is it known whether or not magnitude of induction is sex-linked in humans, as has been shown in animals? Were enzymes in female subjects induced to a higher degree than in male subjects?

FALK (W.H.O.)

The inducibility of microsomal enzymes has been studied on human leucocytes in vitro.(1) They came from 353 healthy human subjects. Before exposure to 20 methyl cholanthrene as inducer the enzyme activity measured by aryl hydrocarbon hydroxylatim was less and showed little variability.

After induction it was shown to vary from 130 - 450%. The lower range was more frequent than the upper range. No informati was given on sex.

Reference (1)Kellermann G. et al Genetic Variation of aryl hydrocarbon hydroxylae in human lymphocytes. Am. J. Human Genet. 25: 327 - 331, 1973.

PERSPECTIVES IN THE ENVIRONMENTAL TOXICOLOGY OF TRACE METALS

KENZABURO TSUCHIYA

Department of Occupational Medicine and Epidemiology, Keio University School of Medicine, Tokyo, Japan

ABSTRACT

The term "environmental toxicology" has come into use in recent years, since environmental pollutions of trace metals and their effects on human health have been recognized. Environmental toxicology differs from industrial toxicology in that, not only does the former often include the latter, but is concerned usually with exposure to trace metals in much smaller doses by larger number of the general population, including children, the aged and the sick.

The use of epidemiological approaches is very important in order to detect the insidious health effects of trace metals on the general population. In light of the significance of these approaches, the following five aspects of environmental toxicology have been chosen for discussion in this paper, with references to a number of reports on each aspect available up to the present time. They are:

1. *Dynamic pathways of trace metals in the ecological environment*
2. *Accumulation of trace elements in human beings*
3. *Dose-response relationship*
4. *Detoxication of trace metals*
5. *Evaluation of unspecific responses in individuals and in groups. Recommendations for further studies which still need to be done concerning each of these aspects are also included.*

Introduction

The term "environmental toxicology has come into common usage in the scientific comminity in recent years as environmental pollutants have been recognized and their effects on the health of man and animals have become the concern of numberous scientists, many of whom are also interested in industrial toxicology. Recent stidies and reviews of environmental toxicolog are well represented by such monographs as "Lead, Airborne lead in perspective," published by the National Academy of Sciences, Washington, D.C., 1972, and Cadmium in the Environment, by Friberg and Associates, 1971. This presentation will be concerned mainly with epidemiologocal methodology evaluatio of the results obtained by epidemiological studies.

The methodology of assessing biological effects of trace metals is classified into three categories, namely animal experiments, experimental studies on humans, and epidemiological studies. Although the methodology of research in the field of metal toxicology has remained unchanged since the beginning of medical science, implication, significance, and meaning of "biological response" have been altered in recent years, particularly after the recognition of health effects on the general pollution due to insidious environmental pollution. The reasons for this change can be ascribed to the following facts: 1) advances in the biological sciences, particularly in biochemistry, molecular biology, and physiology, which have enabled toxicologists to detect minor effects of trace metals on organisms, and 2) exposure of the general population to environmental pollutants, including toxic metals in general, may be much smaller in amount than those having been observed among industrial workers. These factors have contributed significantly to the rising importance of epidemiological studies in metal toxicology.

In this presentation I would like to point out several characteristic features of metal toxicology which have gained prominence over the recent years placing special emphasis on epidemiological approaches. The topics to be discussed are outlined in the table below.

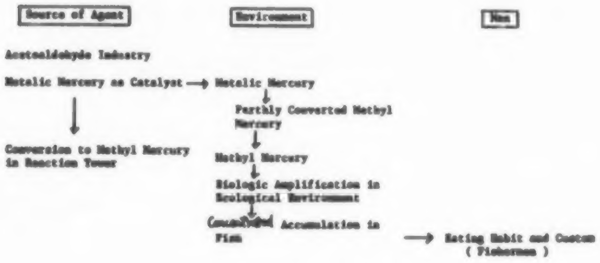
Epidemiological Approaches to
Environmental Toxicology

1. Dynamic pathways of trace matals in the ecological environment.
2. Accumulation of trace elements in human being
3. Dose-response relationship.
4. Detoxication of trace metals.
5. Evaluation of unspecific responses in individuals and in groups.

1. Dynamic pathways of trace metals in the ecological environment.

For detecting the entity of a particular disease, physicians in clinical practice have played an important role. It was they who recognized and reported the first cases of both methyl mercury poisoning (also called Minamata disease) and of Itai-itai disease in Japan. Epidemiological studies which follow such clinical case reports aim to find and confirm, if possible, a factor or factors directly or indirectly associated with the cases of the disease. However, in many instances, the detection of the causative agent has not been as easy as has been the case in well-known communicable disease. It took more than six years before the source and agent of Minamata disease was finally discovered (Kumamoto University, 1968).

Figure 1 Pathway of Methyl Mercury in Ecosystem


Source of Agent
Environment
Man
Acetoaldehyde Industry
Metalic Mercury as Catalyst
Metalic Mercury
Partly Converted Methyl Mercury
Conversion to Methyl Mercury in Reaction Tower
Methyl Mercury
Biologic Amplification in Ecological Environment
Concentrated Accumulation in Fish
Eating Habit and Custom (Fishermen)

As shown in figure 1, the mechanism of the pathway of metyl mercury appears to be simple when seen in retrospective This has brought us important knowledge in environmental toxicology which had never been described in classical toxicology, namely 1) that metallic mercury produces methyl mercury in the process of catalytic reaction in the reaction tower of acetoaldehyde as well as by bacteria in the environment, and 2) that methyl mercury is amplified in environmental aquatic organisms, resulting in high concentrations of the metal in fish eaten by man. As has been clearly shown in the case of methyl mercury, dynamic pathways of other trace metals in the ecological environment, particularly lead, cadmium, zinc, manganese, arsenic and vanadium, should be more rigorously studied in the future. No such studies have been performed thus far. Future studies should include the identification of the types of compounds found in water, soil, plants, animals, and in man.

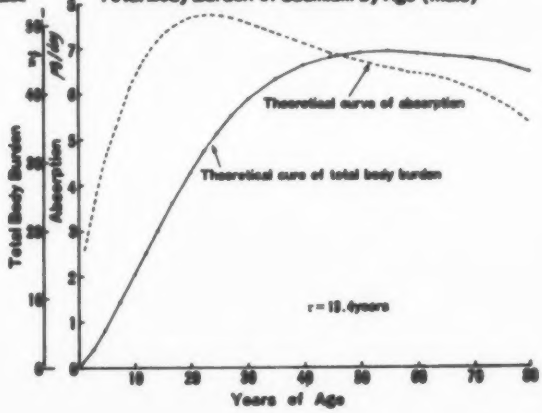
2. Accumulation of trace metals in man

Reports on the accumulation and distribution of trace metals in "normal" men on an international scale have been rather limited. There do exist reports on various metals by Schroeder and Balassa (1961), Tipton and Cook (1963), Tipton, Schroeder, Perry, and Cook (1965) of the U.S.A., on cadmium by Tsuchiya, Seki, and Sugita (1972), also by kimura, Sumino and Kamatani (1970), and on lead by Horiuchi (1970) from Japan. Prospective epidemiological studies on the accumulation of trace metals in the general population would provide us with two vital kinds of information: 1) general background information on the increase or decrease of those trace metals over long periods time (years, decades, etc.) and 2) basic information needed in order to derive biological half times of those metals in man.

It is important to obtain such background information on trace metals in environmental toxicology. If successive observations are made according to lapse of time, an increase of accumulation of lead, for example, in man, may be detected. This would make it possible to anticipate probable effects due to the metal prior to the development of actual health hazards. In order to obtain accurate and precise information on the subject, a sufficient number of autpsies of, if possible, sudden death (since diseases over long periods of time may change the distributions of trace elements) with proper sampling, proper analytical methods and evaluations would have to be performed.

Fig. 2

Total Body Burden of Cadmium by Age (Male)

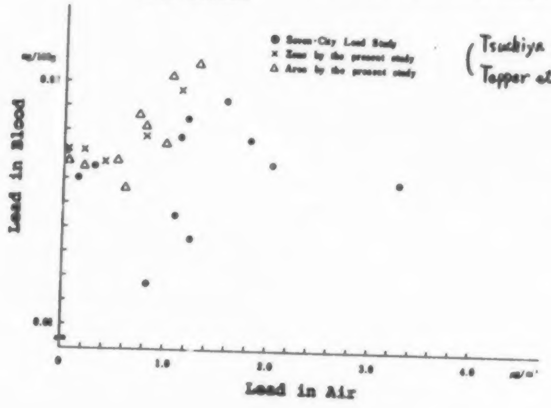


As shown in Figure 2, Tsuchiya, Sugita, and Seki (1972) first utilized accumulation curves of cadmium in various organs by age for deriving Biological half times of the metal for the whole body and for some organs. The reported experimental studies on animals and on man have indicated great discrepancies in the biological half times of the metal. In our study on humans, we found much longer biological half times of cadmium than in those on animal experiments. We believed then, as now, that most of the cadmium absorbed would probably be combined with metallothionein to form "slow components" if the uptake of cadmium is low in amount. Since the biological half times of other environmental metals have not yet been determined, more studies using this kind of approach should be made in the future for that purpose.

3. Dose-response relationship

Since information on dose-response relationship of metal gathered from animal experiments cannot be directly applied to man, epidemiological studies are required, specifically concerning low doses of exposure over a long period of time.

Fig. 3 Blood Lead Levels and Corresponding Mean Air Lead Levels

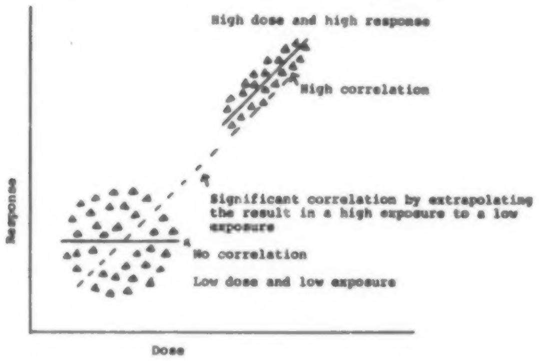


(Tsuchiya et al, 1974
Tepper et al, 1972)

Figure 3 is a combined figure of studies by Tsuchiya et al. (1974) and Tepper (1972), showing the relationship between lead concentration in the air and blood lead concentration. The two studies seem to indicate a fairly good agreement in their results. However, if you look at the dot marks by Tepper, there is obviously no correlation between the level of lead in the air and the blood lead concentration in man, whereas if you look at the cross marks in Tsuchiya's study, they seem to show a correlation within very small ranges of the concentration of lead in the air and of blood lead level. In fact, the correlation was significant with a coefficient of 0.7. In Tsuchiya's study there was no higher lead concentration in the air than 1.5 μg/m^3, while the highest lead concentration in the air in Tepper's study was nearly 4.0 μg/m^3. The correration which was observed in the Tsuchiya study may be correct or incorrect, due to the fact that in that study the subjects were approximately 2,300 policemen who might have been exposed to higher concentrations of lead for longer hours per day than the housewives of the U.S.A. in the Tepper study. Furthermore, it is also possible that the correlation of the two highest points was strengthened merely by coincidence. Also, the difference of lead concentration in blood between the highest and lowest points in the Tsuchiya study was only 1.5 μg/100g. At the present time, therefore, we cannot draw the conclusion that the lead concentration of air between nearly 0 up to 4 μg/m^3 would significantly increase lead concentration of the blood

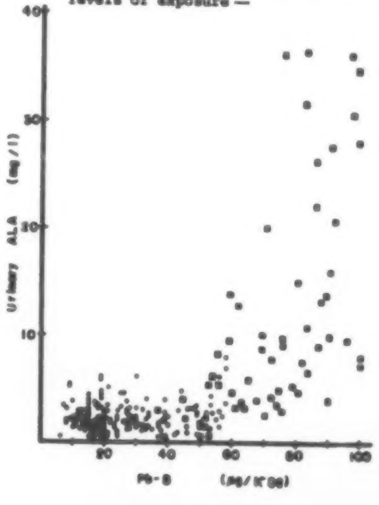
In areas of low exposures one must be very carful in drawing conclusions about dose-response relationship before numberous other observations have been made.

Figure 4 Irrationality of Extrapolation


High dose and high response
High correlation
Significant correlation by extrapolating the result in a high exposure to a low exposure
No correlation
Low dose and low exposure
Response
Dose

Generally, as shown in Figure 4, in "normal" exposure there is little or no relationship because of no response in "normal" or a little higher exposure, and because of analytical errors in measuring both and response. On the other hand, in higher exposures one may obtain a very close correlation. As shown in the figure, when high and low exposures are combined, a straight linear regression is obtained. From these facts I would like to point out here that one should never extrapolate an observation obtained in the higher or lower exposure ranges to evaluate dose-response relationship.

Figure 5 Blood Lead and ALA in Urine
—Dose-response relationship in various levels of exposure —



An example of such a situation demonstrated by avaiable data is shown in Figure 5 (Sakurai, Sugita and Tsuchiya, 1974), which shows a dose-response relationship between blood lead and ALA in the urine in a wide area ranging from low dose to high dose. As indicated in the figure, the response which is ALA concentration in urine (in this case) is constant until lead concentration in blood rises up to about 40-50 µg/100g. This means that there is no correlation in lower doses of lead. In higher exposures, however, a high correlation is observed. In conclusion, here again, to extrapolate would be irrational, as is the case in all biological sciences.

4. Detoxication of trace metals.

In metal toxicology detoxication or adaptation mechanisms have never been resported expect for observations on cadmium exposure in which metallothionein is produced in man and in experimental animals. Metallothionein of cadmium has been considered to be a detoxicating agent which prevents toxic effects of cadmium on the cells. Recently a study by Kimura et al. (1974) demonstrated pertinent evidence to show that cadmium metallothionein has an activity of detoxicating the effects of cadmium.

Figure 6 Relationship between production of 1, 25-$(OH)_2$-D_3 and Cd Metallothionein as well as Cd^{++}
(Kimura, M. et al., 1974)

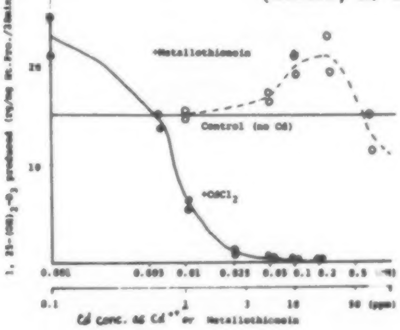


Figure 6 shows a result of one of his animal experiments. In the figure it is clear that vitamin D_3 activity is reduced with the increased ionic cadmium concentration in the kidneys of animals, whereas the vitamin activity remains normal in spite of the high concentration of cadmium which is combined with metallothionein. This kind of detoxication mechanism has never been demonstrated for other metals. However, there have been a few reports which also suggest the existence of detoxication for lead. Tsuchiya in 1954 performed animal experiments in which resistance against lead toxicity was shown in animals pre-treated with lead. More recently, in 1972, a similar observation was made by Yoshikawa. In conclusion I would like to say that more epidemiological studies should be made on industrial workers as well as on the general population exposed to excessive amount of environmental metals in order to discover whether detoxication or adaptation occur.

5. Evaluation of unspecific responses in individuals and in groups.

Since exposures to environmental metals in the general population are low over a long period of time, the effects of these metals are in general insidious and are detected only by observations of groups, not of individuals. Furthermore, very early signs of toxic effects of metals are usually unspecific. For instance, one early sign of cadmium intoxication is proteinuria, but proteinuria due to a number of cases is also observed in the so-called "normal" population with increased prevalence according to age. Very often medical treatment is not required for those people with proteinuria which is not very high in quantity and not attributable to just one specific disease. In some areas in Japan which are known to be cadmium polluted, higher prevalences of proteinuria have been observed than in control areas. Furthermore, proteinuria with low molecular proteins was observed among older people, particularly among females and those over seventy, in non-polluted areas. From such observations one can state that some effects of cadmium, particularly on the kidneys, exist in the polluted areas as affecting a group of people. Nevertheless, if one person with proteinuria and low molecular proteins from that group was isolated, it could not be determined whether that particular individual was affected by cadmium. Insuch a case, only cadmium concentration in the urine could be referred to for differential diagnosis.

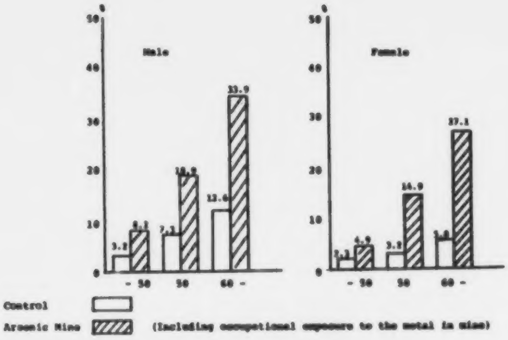


Figure 7 Prevalence of Abnormal EMG Findings in Arsenic Mine and Control Area (Takahashi and Nakamura 1974)

Takahashi (1974), as shown in Figure 7, observed higher percentages of abnormality in the EMG among people older than 50 years of age in a community located near an arsenic mine in comparison with those people living in a control areas. The mine had been closed down more than 20 years preceding the study and some environmental pollution by arsenic was detected in the water, soil, agricultural products, and also in the drinking water in the wells of a few homes. This was because the sludge of a nearby hill along which a river flows was found to contain a very high concentration of arsenic. Biological samples from people in this area did not show eleveted concentrations of arsenic at the time the study was made. Furthermore, skin abnormalities which are characteristic of arsenic poisoning were not found in any individual. This situation is very similar to that mentioned above for cadmium and proteinuria. As shown in Figure 7, percentages of abnormal EMG are higher in the polluted areas than in the control area. It can be said that the area had been polluted and minor effects of arsenic on the health of the inhabitants exist. However, if one individual with an abnormal EMG, that is to say, unspecific response, were to be pointed out from that group, it would not be possible to make the diagnosis that that person is suffering from arsenic poisoning.

Thus, the above mentioned two cases of cadmium and arsenic strongly suggest that toxic metals accelerate the general aging process of man.

Conclusion

In conclution, the recent studies of environmental toxicology have demonstrated various methodological approaches and detected many minor effects of environmental metals on health in comparison with calssical studies in the field of industrial toxicology. In environmental toxicology epidemiological approaches become more and more important, and the evaluation of the results, the most crucial aspect, becomes more and more complex. The primary task of environmental toxicology is to provide the information needed in order to establish environmental standards for toxic metals. To obtain basic information for this purpose we need not only studies of the toxicities of metals on animals and human beings, but especially, more studies to provide the general background of trace metals in the environment and in man. The ultimate goal of environmental toxicology is a clean environment free from pollution by toxic metals. This goal cannot be attained without collaborative studies on an scale which would furnish more precise information on formal pollution by toxic metals in the past, present, and future, and in particular, on the effects they have on the health of the human race.

References

Committee on Biologic Effects of Atomospheric Pollutants, Division of Medical Sciences, National Research Council: Lead, Airbone lead, in perspective., National Academy of Sciences, Washington, D.C., 1972.

Friberg, L., Piscator, M., and Nordberg, G., Cadmium in the Environment, The Chemical Rubber Co., Cleveland, Ohio 44128, 1971.

Horiuchi, K., Lead in the Environment and its Effect on Man in Japan, Osaka City Medical J., 16, 1, 1970.

Kimura, M. et al., Relationship between productions of 1, 25-$[OH]_2$-D_3 and Cd Metallothionein as well as Cd^{++}., F.E.B.S. Letters, Accepted for publication, 1974.

Kitamura, S., Sumino, K., and Kamatani, N., Cadmium concentrations in livers, kidneys and bones of human bodies, Jap. J. Publ. Health, 17, 761, 1970 (In Japanese).

Kumamoto University, Minamata Disease, Study Group of Minamata Disease, Kumamoto University, Japan, 1968.

Sakurai, H., Sugita, M., and Tsuchiya, K., Biological Responses and Subjective Symptoms in Low Level Lead Exposure. Accepted for publication in Arch. Environ. Health, 1974.

Schroeder, H. A. and Balassa, J. J., Abnormal Trace Metals in Man: Cadmium, J. Chron. Dis., 14, 236, 1961.

Takahashi, K. and Nakamura, H., Neurological Examination of Inhabitants in Sasagadani Area of Arsenic Mine, Kankyohoken Report, 32, 1, 1974 (In Japanese).

Tepper, L., and Levin, L. S., Asurvey of Air and Pollution Lead Levels in Selected American Communities, Department of Environmental Health, College of Medicine, University of Cincinnati, Ohio, 1972.

Tipton, I. H., and Cook, M. J., Trace Elements in Human Tissue, II, Adult Subjects from the United States, Health Phy., 9, 103, 1963.

Tipton, I. H., Schroeder, H. A., Perry, H. M., and Cook, M. J., Trace Elements in Human Tissue, III, Subjects from Africa, The Near East and Far Eastern Europe, Health Phys., 11, 403, 1965.

Tsuchiya, K., and Kuwaki, H. A., A Study on Tolerance of Animals to Lead Poisoning, J. of Science of Labor, 31, 291, 1955 (In Japanese).

Tsuchiya, K., Sugita, M., A Mathematical Model for Deriving the Biological Half-Life of Chemicals, Sartryck ur Nordisk Higienisk Tidskrift, Band LIII, sid. 105, 1971.

Tsuchiya, K., Seki, Y., and Sugita, M., Biological Criteria for Exposures to Lead and Cadmium, presented in the 17th International Congress of Occupational Health, Buenos Aires, Sept. 17-23, 1972.

Tsuchiya, K., Sugita, M., and Seki, Y., A Mathematical Approach to Deriving Biological Half Times of Cadmium in Some Organs -- Caluculations from observed accumulations of the metal in organs, presented in the 17th International Congress on Occupational Health, Buenos Aires, Sept. 17-23, 1972.

Tsuchiya, K., Sugita, M., Seki, Y., Kobayashi, Y., Hori, M., and Park, C. B., Study of Lead Concentration in Atomosphere and Pollution in Japan, Accepted for publication in J. of Environ. Quality and Safety, 1974

Yoshikawa, H., Preventive Effect of Pretreatment with Low Dose of Metals on the Acute Toxicity of Metals in Mice, Ind. Health, 8, 184, 1970.

DISCUSSION

MAGE (Denmark)

In view of the very large standard deviation in a spatial lead distribution in the atmosphere shown by Edwards in his Paper, it is not reasonable to expect zero correlation at low Pb levels, since the blood lead level is produced then primarily by food and liquid intake. At high airborne lead levels, the effect of food and drink is submerged and the correlation shines through like the sun through a cloudy sky.

The high correlation data then correctly shows as you even indicate on figure 4, that in the limit as airborne lead goes to zero, the response also goes to zero or a (food-liquid) threshold which is finite but small.

Therefore since the combined model is physically significant, why can't we state that the extrapolation to zero is valid.

TSUCHIYA (Japan)

I did not mean to imply that there is never any correlation in lower exposures. I simply wish to point out that one cannot extrapolate the results obtained in higher exposures which were actually observed to lower exposures without the evidence of actual observations. As is well known, in general, the dose-response relationship in radiation exposure, both dose and response will reach zero but in heavy metal exposures there is no such linear correlation.

JACOBSEN (U.K.)

In your figure 5 there are two types of symbols implying that the data are derived from two studies. I agree that if only the high-dose data were available then it would be unreasonable to extrapolate linearly and thus infer zero response at moderately high exposures. Conversely, if the low-dose data why were available then it would be equally unreasonable to extrapolate linearly and thereby infer a slope close to zero.

Would Dr. Tsuchiya agree, however, that if the data had been obtained in the same study, or if the studies are sufficiently similar in methodology to justify pooling the data, then it would not be unreasonable to hypothesise a sigmoid dose-response relationship from the result shown?

TSUCHIYA (Japan)

I am in complete agreement with your comments.

KJELLSTRÖM (Sweden)

Looking at your data on relation between EMG abberations and arsenic exposure and your discussion about proteinuria and cadmium, it must be concluded that in environmental science conclusions about cause-effect relationships must be drawn from population studies.

Do you agree that it is most unscientific to try to refer unspecific response in an individual to a specific exposure which is sometimes done?

TSUCHIYA (Japan)

I agree that it is most unscientific to try to refer unspecific response in an individual to a specific exposure as is sometimes done. If the incidence of an unspecific response is rather high among an exposed population, it is very crucial to confirm whether the unspecific response in an individual selected from the exposed population is actually caused by the pollutant in question.

ASSESSMENT OF THE INFLUENCES OF ENVIRONMENTAL POLLUTANTS ON CANCER AND OTHER CHRONIC DISEASES

S. S. EPSTEIN

Environmental Health Programs, Case Western Reserve University,
Medical School, Cleveland, Ohio, USA

ABSTRACT

There is now little doubt that many chronic diseases, hitherto regarded as spontaneous, particularly cancer, are caused by environmental pollutants. This realization is heightened by the exponential increase in exposure of the general population to currently used and new synthetic chemicals - and their degradation products in air, water and soil - which, in general, are inadequately characterized toxicologically and ecologically. These considerations apply with even greater emphasis to relatively uncontrolled occupational exposure to a wide range of known chemical carcinogens, in addition to thousands of other toxicologically uncharacterized or inadequately characterized synthetic chemicals.

Current toxicological techniques are relatively insensitive and limited in their ability to detect toxic agents, particularly carcinogens teratogens and mutagens, individually and in various combinations or mixtures realistically reflecting low or ambient levels and patterns of environmental exposure. Similarly, it is generally considered that epidemiological techniques are unlikely to detect environmental pollutants, such as weak carcinogens, unless there are sharp differentials in exposure of the general population, as with cigarette smoking. For widely dispersed agents to which the population-at-large is generally and

Preceding page blank

ubiquitously exposed, such as unintentional or accidental food additives, human experience is unlikely to provide any meaningful indication of safety or hazard. Similarly, it is not possible to develop valid inferences concerning the safety of occupational exposure to particular chemicals or mixtures of chemicals in the absence of an adequate population sample which has been adequately followed up for several decades.

Scientific considerations apart, there are critical deficiencies in legislative and regulatory approaches to environmental pollutants, including conflicts of interest in the generation and evaluation of data, restrictions on open access to data, and lack of qualified representation of a wide range of concerned viewpoints and interest in decision making processes.

1. Introduction

Although the term pollutant is often pejoratively restricted to synthetic industrial chemicals, there is a wide range of other chemical pollutants. These fit into four broad categories. The first group consists of natural chemicals in excess, such as nitrates and nitrites, which are normal dietary components. Additionally, these particular chemicals can interact with amines, natural dietary constituents, yielding nitrosamines, which may be carcinogenic, mutagenic and teratogenic at trace levels (Lijinsky & Epstein [1]). Natural fungal or plant toxins in crops comprise the second group of chemical pollutants, of which aflatoxins and cycasins are notable examples. The yields of these toxins can generally be influenced by technological factors, such as conditions of harvesting, storage and processing. The third group consists of complex organic and inorganic mixtures, such as community air and water pollutants and occupational pollutants,such as coke tar pitch volatiles, which comprise a wide range of undefined as well as partially defined components. Finally, there is the group of synthetic chemicals-agricultural chemicals, notably pesticides and fertilizers; food additives, which may be *intentional*, such as antioxidants and dyes, or *accidental*, such as pesticides, heavy metals and plasticizers; fuel additives; household chemicals, and industrial chemicals. Most of these chemicals are petroleum-based, petroleum now being the basic stock for synthesis of the great majority of all organic chemicals.

Pollutants may induce a wide range of adverse biological effects in man, which are generically and collectively termed toxicity. Acute or chronic toxicity *per se* may be expressed in fetal, neonatal, perinatal, childhood or adult life, in effects ranging from impairment of health and fitness to mortality. More specific manifestations of chronic toxicity include carcinogenicity, teratogenicity and mutagenicity. The possibility that chronic toxicity is also manifest in immunological impairment or in psycho-behavioral disorders has yet been barely explored. Some pollutants may induce one or more of these types of toxicity. Pollutants or their chemical precursors may also interact *in vitro* and *in vivo* to produce otherwise unanticipated synergistic toxicity. Synergistic effects can also result from interactions between particular pollutants and otherwise harmless and common environmental chemicals.

amoral. Illustratively, the carcinogenic effects of bis-chloromethyl ether and vinyl chloride, and the neuropathic effects of organic solvents, such as methylbutylketone, could easily have been determined by simple and standard animal tests, rather than by human experimentation.

6. Evaluation of the Benefit-Risk Calculus

Since World War II, there has been an exponential and, largely, unregulated increase in the numbers and quantities of synthetic organic chemicals manufactured and used in industrialized countries. The claimed needs to use increasing numbers of new synthetic chemicals makes it essential to recognize and critically evaluate carcinogenic and other human and environmental hazards with regard to the real or alleged matching benefits they confer. Such costing must be weighted by factors including the persistence and environmental mobility of the chemical, the size of the population exposed, and the reversibility of the adverse effect. Total national monetary costs in the U.S., both direct and indirect, from cancer are estimated to be approximately $15 billion annually (National Cancer Program [10]); these costs have hitherto been largely externalized or discounted. As the majority of human cancers, both in the general population and in occupational groups, are now considered to be due to chemical carcinogens and hence preventable, there should be clear economic, besides other, incentives to reduce the environmental and occupational burden of chemical carcinogens.

Carcinogenic hazards from a particular synthetic chemical need not necessarily be accepted even when matching benefits appear high, as equally efficacious but nonhazardous alternatives are usually available. The mandatory criterion of efficacy, once extended from therapeutic drugs to other synthetic chemicals, such as deliberate and accidental food additives, feed additives and pesticides, may well simplify such equations, especially for hazards from synthetic chemicals with no demonstrable benefits for the general population. The imposition of a requirement for broad social utility may even further simplify the benefit-hazard equation. Such concepts have been recently emphasized with regard to food additives by a leading industrial representative who recommended that additives be excluded from products unless they either significantly improve the quality or nutritive value of the food or lower its costs as well as being safe (Kendall [11]). Claims that occupational carcinogens serve industrially unique purposes, must be examined critically by economically disinterested experts with particular recognition of the attendant and generally externalized human costs and the lack of economic incentives to develop similarly efficacious and non-hazardous alternatives. In the absence of such alternatives, consideration must be directed to the possible banning of the manufacture and use of the carcinogen or to restrict its use to closed systems which are continuously monitored with instrumentation of maximal sensitivity, and with automated and visible read-outs.

Inherent in toxicological and regulatory philosophy and practice is lip service to the concept of balancing benefit, and benefit to the public not to industry, against risk, and risk to public health or environmental integrity and not economic risk to industry. If the chemical in question does not serve a broad socially and economically useful purpose for the general population, why introduce it and force the public-at-large to accept potential hazards without general matching benefits? Such questions should be vigorously directed to carcinogenic, and otherwise hazardous, cosmetic food colouring agents, in particular, and to all food additives, in general. Claims have recently been made (Gehring et al [12]) that requirements for pre-testing of chemicals prior to their introduction to commerce are acting as disincentives to industrial innovation. These claims have been particularly directed to the manufacture of pesticides (Naegele [13]). Apart from the fact that such claims are predicated on the legitimacy of externalizing public health hazards and costs, they do not bear critical scrutiny even from narrowly defined economic viewpoints. A telling critique of such claims has been expressed by a leading industry spokesman who stated that he — "emphatically (takes issue with the line of reasoning that) escalating regulatory demands have made the cost of research and development prohibitive, thus drying up any incentive to go develop new agricultural chemicals...

"... In the first place (argued Dr. Sutherland), new regulations imposed since the creating of EPA affording better protection to fish and wildlife were overdue. More important is the changing aspect of the marketplace, particularly in the pesticide area. Growers now have available to them many first-rate products... many of these are quite inexpensive. What the chemical people are really telling you is that while research costs continue to rise, to come with still better compounds costing no more money than what's already being sold is a tough proposition...; the companies with weak research organization, a shaky financial position, are dropping out. They would rather have FDA and EPA take the rap rather than acknowledge the overall problem" (Sutherland [14]). In any event, information in 1973 suggests that the profitability of pesticides and their development is again rising (Bennett [15]).

It has now become axiomatic that there are major defects in decision making processes in regulatory practices. It is clear that the democratic system of checks and balances is largely absent from current regulatory practice (Epstein [2]). Apart from limited post hoc recourse, the citizen, consumer and working person, and those who represent his or her interests, scientifically and legally, are virtually excluded from anticipatory involvement in decisions vitally affecting them. The concept of matching benefits against risk has been generally applied to maximise short-term benefits to industry, even though this may entail minimal benefits and maximal risk to the consumer. While such an approach is of course detrimental to the consumer, it is also often detrimental to the long-term interests of industry, which may suffer major economic dislocation when hazardous products, to which it has improperly developed major commitments, are belatedly banned from commerce. Such problems are in large measure attributable to crippling constraints which have developed and which still dominate the decision making process within regulatory agencies. Responsibility for these constraints must be shared with regulatory agencies, by the legislature, by the scientific community, and by citizens, consumers and workpersons who have not yet developed adequate mechanisms for protecting their own vital rights.

It is perhaps no coincidence that the attacks on the Delaney Amendment are mounting at a time when the food chemical industry is poised for a major expansion. The chemical industry predicts that sales of chemical additives are expected to grow from $485 million in 1970 to $750 million by 1980. In providing a framework for evaluating potential hazards of these additives, the Delaney Clause simply ratifies the prevailing expert opinion in the National Cancer Institute and in other professionally qualified groups that there is no practical method to determine safe dietary levels for a carcinogen (Saffiotti [16]; Epstein [17]). Changing the Delaney Clause to allow regulatory discretion to set tolerances for carcinogens is, therefore, not only scientifically inappropriate, but, administratively foolhardy.

Conflicts between crucial social goals, such as reduction in the incidence of human cancer due to environmental and occupational carcinogens, and powerful concentrated economic interests are often joined on supposedly scientific grounds. Illustrative, are the current U.S. cancellation hearings on Aldrin/Dieldrin which have largely focused on the significance of carcinogenicity tests in rodents as a basis for risk extrapolation to humans (Epstein [18]). Industry and its consultants, generally toxicologists without primary expertise in carcinogenesis and pathology, have at varying times advanced the following illustrative mythologies:

1. The mouse hepatoma is not a true neoplasm but a regenerative nodule.
2. Hepatomas induced by mice, illustratively by persistent organochlorine pesticides, are "compound-dependent" and will regress following cessation of test exposure.
3. The mouse hepatoma is a benign neoplasm and that agents inducing it should be classified as "tumorigens" and not carcinogens. It is thus argued that standard regulatory practices for carcinogens are inappropriate for "tumorigens".
4. Transplantability of the mouse hepatoma does not necessarily establish its neoplastic nature.
5. Dieldrin is a "species-specific" carcinogen for the mouse and the mouse is endowed with a unique hypersensitivity to chemical carcinogens. It is thus argued that data from mouse carcinogenicity tests have little or no human relevance.
6. Human experience, based on 826 workers of whom only 35 had been followed-up for over a decade, has proven that Dieldrin is not carcinogenic to humans.

In fact, the published literature clearly establishes that Dieldrin is carcinogenic in several strains of mice, at the lowest dose yet tested, 0.1 ppm, producing metastasizing hepatocellular carcinomas in addition to a variety of neoplasms at other sites (Epstein [18]). Additionally, more limited studies clearly establish the carcinogenicity of Dieldrin in the rat, in which hepatocellular carcinomas in addition to carcinomas of other organs have been demonstrated. It must be emphasized that Dieldrin is highly stable and persistent, that human lipid levels range from 0.5 to 2.9 ppm, that tolerances for Dieldrin, petitioned by Shell, in various animal food products range from 0.1 to 0.3 ppm, and that on the basis of such petitions and existing tolerances on raw agricultural commodities, Dieldrin levels in a standard diet have been calculated to be 0.04 ppm.

It is our clear professional responsibility to expose the unscientific nature of the industrial mythology on toxicology, in general, and on carcinogenesis, in particular, typified in the Aldrin hearings. Embattled agencies, such as The Environmental Protection Agency, and public interest groups can not be expected to unaidedly bear the onerous burden of protecting the public health. Pressures on agencies can subvert implementation of standards and of the total regulatory process. This has been well recognized in statements such as the following: "It is the daily machine-gun like impact on both agency and its staff of industry that makes for industry orientation on the part of many honest and capable members, as well as agency staffs" (Landis [19]). Nevertheless, appropriate reforms in agency-industry relationships have yet to be developed. Reforms apart, it is clear that decisions on the use of toxic agents, such as carcinogenic chemicals in consumer products and in the workplace, must be made in the open political arena and on the basis of the evaluation of scientific data that is both expert and unbiased. Industry must be encouraged to avoid preoccupation with short-term economic interests and the development of premature commitments to products and processes which have not been adequately tested by competent and independent investigators. Such approaches will minimize or preclude the possibility of economic dislocation which would otherwise ensue when subsequent challenges necessitate the belated withdrawal of the product or process from commerce and the workplace. Such approaches also reflect recognition of the consonance of long-term industrial interests and broadly-based societal goals and values.

Acknowledgements

Section 6 of this paper is largely based on an M.S. "Environmental Determinants of Human Cancer." Epstein, S.S. Cancer Res. in press.

References

1 LIJINSKY, W. and EPSTEIN, S.S., "Nitrosamines as Environmental Carcinogens." *Nature*, 225, 21 (1970).

2 EPSTEIN, S.S. "Environmental Pathology: A Review." *Am. J. Path.*, 66 , 352, (1972).

3 DUNHAM, L.J. and BAILAR, J.C., "World Maps of Cancer Mortality Rates and Frequency Ratios." *J. Nat. Cancer Inst.*, 41, 155 (1968)

4 HIGGINSON, J., "Present trends in Cancer Epidemiology," Proc. 8th Canadian Cancer Res. Conf., 1969.

5 MORGAN, B. AND REPKO, J.D. National Institute of Occupational Safety and Hygiene (NIOSH) Contract Report, HSM-99-72-123, 1974.

6 SEPPALAINEN, A.M. In, "Behavioral Toxicology: Early Detection Occupational Hazards". eds. C. Xintaras, B.L. Johnson and I. de Groot, NIOSH, HEW, In Press, 1974.

7 "EPA's Position on the Health Implications of Airborne Lead", November 28, 1973.

8 EPSTEIN, S.S. Testimony before the U.S. House of Representatives Committee on Education and Labor, Select Subcommittee on Labor, April 25, 1974.

9 INNES, R. *et al.*, "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note." *J. Nat. Cancer Inst.* 42, 1101 (1969).

10 *NATIONAL CANCER PROGRAM*. "The Strategic Plan". D.H.E.W. Publication No. NIH 74-569, January, 1973.

11 KENDALL, D.M. "A Summary of Panel Recommendations." Report of a Panel on Food Safety to the White House Conference on Food Nutrition and Health, (19),22 November, 1969.

12 GEHRING, P.J., ROWE, V.K., & McCOLLISTER, S.B. (Dow Chemical Co.) "Toxicology: Cost/Time", *Fd. Cosmet. Toxicol.* 11, 1097 (1973)

13 NAEGELE, J. (Dow Chemical Co.). Testimony to U.S., Congress, House, Committee on Agriculture, *Hearings on Federal Environmental Pesticide Control Act of 1971*, 92nd Congress, 1st session, Washington, D.C.: U.S. Gov. Printing Off., 1971.

14 SUTHERLAND, G.L. (American Cyanamid). "Agriculture Is Our Best Bargaining Tool," *Farm Chemicals*, 135, 44 (1972).

15 BENNETT, I. "Preface," *Pesticides Monitoring Journal*, 1: no. 1, (June, 1967).

16 SAFFIOTTI, U., "Comments on The Scientific Basic for The 'Delaney Clause'". Preventive Med. 2, 125 (1973).

17 EPSTEIN, S.S., "The Delaney Amendment." Preventive Med. 2, 140 (1973).

18 EPSTEIN, S.S. Testimony at Cancellation Hearings on Aldrin/ Dieldrin (EPA & EDF vs. Shell), March, 1974.

19 LANDIS, J. Report to President-elect Kennedy, 1960.

DISCUSSION

van ROOYEN (South Africa)

One is glad that the question of decision-making was raised. There are other aspects that need consideration. During the course of this conference, we have had several papers on the effects of environmental factors and more particularly emissions from specific factories on populations at risk. With few exceptions no mention was made of the requirements placed on them by air pollution control authorities. Were these emissions completely uncontrolled, partially controlled, or by the best practicable means? Surely before-and-after studies to evaluate the effect of control measures are imperative.

One also suspects that pollution is being exported to developing countries because of the stringent measures in highly developed countries. The former must accept this as raising of their national product to control poverty, malnutrition and ignorance is paramount. It is thus necessary that these countries should know how effective control measures are.

EPSTEIN (U.S.A.)

I agree with the concepts expressed. Developed countries have a clear responsibility to avoid "exporting" pollution to developing countries. It is hoped that the latter will be encouraged to appreciate the long-term economic, besides public health air environmental costs of "importing" pollution. It is, however, clear that the priorities influencing decision making processes and the degrees of checks and balances in such processes will vary widely from country to country.

van der KREEK (Netherlands)

Professor Epstein, you complemented the Swedish Government for the ban of synthetic colours for use in food products, but I am informed that this ban is not a complete ban, but a ban of some food colours in some food products and therefore is not a decision of principle, but a decision based on toxicological and technological principles.

EPSTEIN (U.S.A.)

The Swedish "Ban" is conceptual and indicates future policy that cosmetic or coloring food additives will be disallowed in future in the absence of unquivocal data on safety and on critical societal efficacy.

KIELLSTRÖM (Sweden)

I believe on the contrary that the Swedish decision was very important in principle, but perhaps not very important toxicologically. All colour additives to food are banned in principle and will only be accepted after thorough evaluation. This is an example of the "negative proof philosophy" that I mentioned here earlier which means that synthetic chemical products should be deemed deleterious to health at any concentration as long as no data are available.

EPSTEIN (U.S.A.)

I thank the speaker for his clarification of this important question.

SERWER (U.N.E.P.)

I am sympathetic to what I take to be two of your fundamental points: prior evaluation of efficacy and decentralization of decision-making. In practice, however, there may be a contradiction between these two "desirables." Prior evaluation would remove decisions from the market place, where they are at least decentralized if not well informed. If provision were not made for opening up decision-making on efficacy - and there are practical limits to doing so - your proposal might in fact cause the situation you deplore to deteriorate further.

EPSTEIN (U.S.A.)

The concept of "freedom of choice" in the market place is a myth. The consumer has no options but to purchase products "accidentally" contaminated with a wide range of chemicals, such as Dieldrin, of which he is not informed and for which he is not informed. Free choice implies labelling of ingredient and contamination concentration, hazards and benefits.

TABLE II. The Distribution of EEG Wave Abundance in Selected Frequency Classes as Per Cent of Total for Five Minutes of Recording.

Treatment	11-50 Hz Mean ± S.E.	5.9-10 Hz Mean ± S.E.	1.5-2.9 Hz Mean ± S.E.
Control	26.1 ± 2.3	19.5 ± 1.3	22.6 ± 1.7
2,4-D	**45.5 ± 1.8	*16.7 ± 1.2	*14.3 ± 1.0
Lindane	29.7 ± 1.5	*16.4 ± 1.0	22.6 ± 1.0
Dieldrin	31.9 ± 2.4	18.8 ± 1.7	*19.3 ± 1.2
Parathion	30.2 ± 2.4	19.8 ± 0.9	24.3 ± 1.3
Toxaphene	*35.0 ± 2.8	18.4 ± 0.9	*19.0 ± 1.1
Carbaryl	**50.6 ± 2.1	*17.0 ± 0.5	**12.1 ± 0.9

**$p < 0.01$
*$p < 0.05$

Similarly, zero potential crossover (ZPC) rate/5 second epoch is increased in the EEG of animals showing an increase abundance of higher frequencies as seen in Table III. More interesting is the increased variability of this parameter and the patterning (as indicated by trend analysis) of the variability. The increase in the coefficient of variation is statistically significant for 2,4-D and carbaryl and nearly so for toxaphene. When one plots the counts per epoch in a bar graph, it is apparent that the significant trend represents a sinusoidal pattern with a period of 30-35 seconds.

We felt sufficiently encouraged by the results obtained with the monkeys to proceed with the second phase of the original objective, viz., application of the methodology to human studies. The monkey research is continuing with the application of other time-series analyses, e.g., cross and auto correlation, but I would like now to describe the portable EEG developed and constructed in conjunction with Dr. Jacob Kline, Director, University of Miami Medical Instrumentation Laboratory, School

[1] Phencyclidine hydrochloride, Parke, Davis & Company, Detroit, Michigan
[2] Sodium thiamylal, Parke, Davis & Company, Detroit, Michigan

TABLE III. Characteristics of Zero Potential Crossover (ZPC) Rate During Five Minutes of EEG Recording.

Treatment	ZPC/Epoch Mean ± S.E.	C.V. Mean ± S.E.	Trend Mean Successive Square Diff. / Variance Mean ± S.E.
Control	19.7 ± 1.9	23.0 ± 2.0	2.0 ± 0.2
2,4-D	**28.9 ± 1.6	*31.1 ± 2.3	*1.5 ± 0.1
Lindane	18.8 ± 0.8	22.2 ± 1.1	2.2 ± 0.1
Dieldrin	19.5 ± 1.4	22.4 ± 1.2	2.0 ± 0.1
Parathion	21.1 ± 1.2	22.8 ± 1.5	1.9 ± 0.1
Toxaphene	24.2 ± 1.6	26.3 ± 1.7	1.6 ± 0.2
Carbaryl	**33.4 ± 1.7	*28.6 ± 0.8	*1.3 ± 0.1

**$p < 0.01$

*$p < 0.05$

of Medicine, Miami, Florida, U.S.A. The recording unit has a self-contained battery pack, measures 40 x 40 x 30 cm, and weighs 9 kg. The monitoring oscilloscope is a standard Tektronix 211 and the tape recorder is a standard Sony stereo cassette recorder, TC-124. The input stages of the instrument are high performance differential instrumentation amplifiers in an integrated circuit package. It performs balanced differential measurements with high common mode rejection (CMRR = 106 dB at gain of 100 from DC - 100 Hz, with source unbalance of 1000 ohms).

The second integrated circuit stage is a standard operational amplifier designed with moderate gain to provide sufficient signal level to the four input multiplexer integrated circuit. Control of the multiplexer is accomplished by a 7200 Hz timer clock pulse. The three channels of EEG are multiplexed on one channel of the stereo cassette tape. The timer clock pulse is simultaneously recorded on the second channel to be used in demultiplexing upon playback. This arrangement compensates for differences in tape speed between units. A demultiplexing playback unit was also constructed for playing back the recorded information through the Dynograph, into the data processing system.

Two recording units are in the field at the present time. Agricultural pesticide workers are being recorded before, during, and at the end of the season. The procedure consists of placing the subject on a cot, affixing the scalp electrodes, and after assuring the presence of a good trace on the oscilloscope monitor, obtaining 15 minutes of recording with the subject relaxed and eyes closed. Tapes are then mailed to the laboratory for processing.

It is too early to make comparative observations between pre- and post-exposure EEG's. However, Table IV shows the interval analysis results on six human subjects obtained with this system.

In conclusion, quantitative EEG measures have disclosed changes in monkeys exposed to low levels of pesticides for three years. The animals have displayed no signs of toxicity, and have reproduced each season bearing viable offspring at a rate comparable to our non-treated colony. Our efforts to date have concentrated on the feasibility of the methodology and development of the portable system. Effort is now being concentrated on application of a battery of time series analytical techniques which can be performed on the three channels of EEG described.

TABLE IV. Awake EEG Interval Analysis of Six Subjects Recorded in the Field with Portable Instrument.

Zero Potential Crossover		Frequency Distribution (% of Total Waves from 0.5-50 Hz)			
Waves 5 Sec Epoch	C.V.	Beta 13-50 Hz	Alpha 7.7-12.5 Hz	Theta 4 < 8 Hz	Delta < 4 Hz
		(Mean ± S.E.)			
72.6 ± 7.2	9.5 ± 1.6	64.3 ± 3.7	24.6 ± 2.9	9.8 ± 1.4	1.1 ± 0.3

References

1 DÉSI, I., FARKAS, I., KEMÉMY, T., "Changes of central nervous function in response to DDT administration", Acta Physiol. Acad. Sci. Hung., 30, 275-281 (1966).

2 SPECK, L.R., MAASKE, C.A., "The effects of chronic and acute exposure of rats to endrin", A.M.A. Arch. Ind. Health, 18, 268-272 (1958).

3 VAN GELDER, G.A., SANDLER, B.B., BUCK, B., MALAND, J.B., KARAS, G.G., "Behavioral and electrophysiological effects of dieldrin in sheep", Ind. Med. Surg., 38, 64-67 (1969).

4 HOOGENDAM, I., VERSTEEG, J.P.J., DE VLIEGER, M., "Electroencephalograms in insecticide toxicity", Arch. Environ. Health, 4, 86-94 (1962).

5 METCALF, D.R., HOLMES, J.H., "EEG, psychological, and neurological alterations in humans with organophosphate exposure", Ann. N.Y. Acad. Sci., 160, 357-365 (1969).

6 SANTOLUCITO, J.A., MORRISON, G., "EEG of Rhesus monkeys following prolonged low-level feeding of pesticides", Toxicol. Appl. Pharmacol., 19, 147-154 (1971).

7 WALTER, W.G., "An automated flow frequency analyzer", Electron. Engg., 16, 9 and 236 (1943).

8 DROHOCKI, Z., "L´integrateur de l´electroproduction cerebrale pour l´electroencephalographie quantitative", Rev. Neurol., 80, 619-624, (1948).

9 RUSH, S., DRISCOLL, D.A., "EEG electrode sensitivity - An application of reciprocity", IEEE Transations on Bio-medical Engineering, 16, 15-22 (1969).

10 KLEMM, W.R., HALL, C.L., "Electroencephalographic pattern abnormalities in dogs with neurologic disorders", Am. J. Vet. Res., 33, 2011-2025 (1972).

DISCUSSION

HAIDER (Austria)

Did you use computer analysed evoked potentials and slow potential changes in your studies? In our studies with implanted electrodes in rats we could demonstrate changes in evoked potentials produced by pesticides.

SANTOLUCITO (U.S.A.)

We have used evoked potentials in animal studies. We have also found them useful, for example in a study with hexachlorophene-treated monkeys, it was possible to demonstrate visual evoked response changes at doses below that required to produce the typical brain lesion.

We are currently using evoked potential measurements in a study of a series of carbamate pesticides.

At present time, we have not attempted this in the field for human studies utilizing the portable EEG.

2395

UNTERSUCHUNG DER GESUNDHEITLICHEN WIRKUNGEN
HEALTH EFFECTS STUDIES
ETUDES DES EFFETS SUR LA SANTE
STUDI DEGLI EFFETTI SULLA SALUTE
ONDERZOEKINGEN NAAR GEVOLGEN VOOR DE GEZONDHEID

(Continued)

Vorsitzender - Chairman - Président - Presidente - Voorzitter

S. HERNBERG (Suomi)

INTERNAL POLLUTION - OUR FIRST PRIORITY
A REVIEW OF THE STUDIES OF THE SPECIAL COMMISSION ON INTERNAL POLLUTION

PETER BEACONSFIELD[+], NORMAN BORLAUG, A. CARPI DI RISMINI,
SIR HANS KREBS, SIR RUDOLPH PETERS AND REBECCA RAINSBURY

Special Commission on Internal Pollution, BMA House, London, UK

+ Royal Free Hospital, London, UK

ABSTRACT

Pollution is the result of man's unwillingness or inability to control his present overpopulation, over-exploitation of natural resources, and over-production of many indestructible goods.

However, attacking environmental pollution will be self-defeating if we disregard man's continuous and progressive pollution of his own milieu interieur - this is what we have termed internal pollution.

Internal pollution is brought about in three ways: by the ingestion and inhalation of the products of the already polluted external environment; by daily intake of chemical additives and impurities prepacked in food; and by the vast number of medicaments taken regularly, and more often than not unnecessarily.

We resolved to consider the present use of chemicals under four broad headings - medication, food additives and colourants, agricultural aids, and household goods; and to relate their respective uses to the responsibility shared by the producers, the consumer, the government regulatory agencies, and the biomedical professions.

In the last year and a half we have examined the field of

Preceding page blank

medications and started our inquiries into food.

The general impression was, particularly since thalidomide, that there is something wrong with the tests, but our investigations do not bear this out. We find the tester and the physician to be the guilty parties.

Testers succomb to human weaknesses of inefficiency and lack of conscientiousness, physicians are ill informed.

Overprescribing and polypharmacy are the twin sins.

Finally, the patient may have unsuspected sensitivity or may be ignorant enough to believe that doubling the dose must double the benefit.

As the whole field of medication is in the control of experts this is one of the aspects of internal pollution capable of solution within the framework of our present technical and economic possibilities.

Pesticides, fertilizers, and other crop and livestock improvers have come into almost universal use. Concern has been expressed about the long-term risks some of these chemicals entrain. When evaluating this, and always looking to increase the benefit: risk ratio of such agricultural aids, it must be remembered that their use should be discussed within the context of the nutritional status of the population needing to be fed.

Preservatives, packaging aids, and so forth, are the result in large measure of modern economic dictates concerning demand and supply, storage and distribution. The public needs and deserves to be better informed about what is done to the food supply, and why.

We realize that an urgent need exists for clearer understanding of the medical, social, and economic benefits and risks that accrue from the application of science and technology and the use of chemicals in today's world, and better guide lines for decision-making.

But even where fully-tested and established drugs are concerned, most of the adverse drug reactions are the direct result of the indiscriminate and over-indulgent prescribing habits of physicians who often rely solely on advertisers' copy for their information about the use of the drugs. Doctors are lamentably ill-instructed in clinical pharmacology, a hardly-recognised speciality for which there is little or no formal training.

The medical curriculum for the past 100 years has been designed to elicit diagnosis, for until recent times diagnosis was all we could offer the patient apart from surgery. Drugs were few and their mode of action, even when curative, was ill-understood. Now drugs are many and potent and their method of action and interaction must be known by the prescriber. Although this fact is recognised, few medical schools give any formal training in the speciality, and fewer still have academic departments of clinical pharmacology. Courses in clinical pharmacology and therapeutics running in parallel with clinical medicine are rare, and those who design and run them are thought of as second-class citizens by their colleagues - whether these are general physicians or academic pharmacologists. The need for this speciality is underlined by the fact that the rate of introduction of new therapeutic and prophylactic agents during the last 30 years has almost entirely outdated the knowledge of a doctor who graduated before then. Polypharmacy has now become the rule instead of the exception; certain hospital surveys have identified patients taking up to 30 different preparations a day. Small wonder they develop new diseases, and who is to say whether their symptoms are caused by the disease or the drug combination?

Since the whole field of medication is in the hands of experts and is therefore amenable to control, the cavalier attitude of the medical profession is inexcusable. In fact medication is the aspect of internal pollution most easily dealt with in the framework of our present technical and economic possibilities.

Food

The use of chemicals in the food industry has had even more far-reaching effects on Western society's economy than has the concept of positive health. More people eat, and they eat a greater diversity of foods in a greater number of places than ever before. Food is produced in one place, processed in another, sold in a third, and retailed elsewhere again. No longer do the seasons dictate the menus of the developed countries. We have what we want when we want it, and without chemical help, most of this would be impossible.

The economic implications of all this are immense. Whole new industries employing hundreds of thousands of people have been created; farming itself has been modified to produce a crop of maximum suitability and convenience for harvesting and packaging.

A distinction must be drawn here between those chemicals which are valuable in improving the product or in preserving it better, and those which are added purely and simply for profit. It is one thing to add a preservative to give a good product a better shelf life; but it is nothing other than sharp practice to feed a pig a chemical compound which will cause it to retain water to make it weigh more in the market place. SCIP was told that one well-known manufacturer puts up to 20 different chemical additives into his pork pies. Nowadays this is the rule rather than the exception. We may well ask - why?

At present few people realise the degree of adulteration undergone by the food they buy. We believe that in addition to the obligation of food manufacturers to put dates on their packages, which has only recently become mandatory in most countries, all the ingredients and their proportions should similarly be detailed. The consumer needs to be educated to understand and use this information to his best advantage.

The Green Revolution

Pesticides, fertilisers, and other agricultural or livestock improvers have now come into almost universal use. These, together with genetically-improved crops, have produced a new concept - the farming equivalent of "positive health" - the so-called "green revolution". It now takes less manpower to produce more food from a given acreage in a greater diversity of conditions. However, all this is only with the expenditure of more energy for the same tonnage of production. And just as consumers need even greater quantities of chemicals to maintain their standard of living, so intensely-farmed soils come to rely more and more on chemicals to make up for their depleted structures.

However, in all evaluations of "agribusiness" it must be remembered that these 20th century farming aids have to be seen in the context of the nutritional status of the population needing to be fed. We all know about the dead fish in the Baltic and Lake Michigan, but what would happen if DDT were not used in Ceylon? Once again, the point is the same as it is in the matter of "positive health": what benefits do we demand and what risks are we prepared to run for them?

Closing Comments

We should like to stress again that there is practically nothing about pollution - whether internal or external - which is not already known. We know what pollution is, we know how pollution takes place, and we know who does the polluting. SCIP feels that we should now be concentrating more effort into uncovering the circumstances which at present guarantee that such pollution is inevitable, and could remain so.

In our view, safety as a concept is inaccurate, and "safe" products do not exist. The use of this epithet to describe any chemical is wrong and misleading. The World Health Organisation itself is not above criticism for publishing technical papers referring to such mindless concepts as "Safe Use of Pesticides". We must learn instead to talk in terms of benefit and freedom from risk, when it is accepted that substances like DDT can be dangerous but that without their judicious use millions would starve in many parts of the world.

Up to the present, few people have understood that the comfortable life-style of the industrialised world entails its own risks, and that those risks may not be generally known. A man getting into his car to drive to work accepts - albeit subconsciously - that there is a definite statistical chance of his becoming one of the eight million injured or 250,000 killed annually on the roads of the industrialised world. Yet the same man sitting down to dinner does not even consider that his pre-cooked TV repast, bought at the local supermarket, could entail any risk. It is wrong that he should continue in this state of uninformedness. He has a right to know so that he himself can decide whether any risk is worth taking. A separation of what can from what can't be done within our present technological and economic capabilities has to be made. In the case of the pharmaceutical industry, for instance, we consider that the tests applied to new compounds are as good as modern knowledge and technology permits, but that this does not necessarily mean they are done as well as they could be. It is perfectly possible to remedy this, just as it is equally possible for the medical profession to improve its knowledge of the drugs it so freely and generously dispenses. We have seen how necessary it is for doctors to be trained to prescribe: it is not enough to let the advertisers' copywriters do it for them. So far as food and agriculture are concerned, up to the present no clear distinction has been drawn between chemicals used to improve quality and quantity of food production and those used solely to increase producers' profit margins at no price advantage to the consumer and at a possible risk to his health.

The value of many goods, particularly in the domestic consumer industry, is overstressed by advertising; the public is conditioned just as effectively as any Pavlovian dog by the sheer weight and repetitiousness of the advertising copy thrust upon it.

At present the consumer is exploited through his technical ignorance. SCIP realises that an urgent need exists for clearer understanding of the medical, social, and economic benefits and risks that accrue from the application of science and technology and the use of chemicals in today's world, and better guidelines for decision-making.

The purpose of our endeavour is to enable us to inform and instruct the citizen on the causes of internal pollution and what is entailed in trying to remedy them. In a free society, at the end of the day it is the citizen who finally decides what kind of life he wants. It is our responsibility as scientists to see that he has the necessary knowledge to make the right decision.

Unfortunately, meetings such as the three this summer do not achieve this objective; they satisfy the egos of a small scientific élite, but do nothing for the wider public of which we are also members. It is up to us to start a dialogue with our fellow citizens rather than conduct monologues among ourselves; otherwise it will begin to look as if the sheer number of speeches, like the sheer number of diverse laboratory tests on a new drug, will reveal this air of purposefulness to be an illusion.

A COMPREHENSIVE TOXICOLOGICAL LIMITATION OF TOXIC SUBSTANCES IN THE ENVIRONMENT. FUNCTIONAL AND METABOLIC CRITERIA OF NOXIOUS ACTION

N.F. IZMEROV, I.V. SANOTSKY

Institute of Labor Hygiene and Occupational Diseases, Moscow
USSR

ABSTRACT

Methods based on the determination of the adaptability limits of the organism and on metabolical criteria may be regarded as a methodological basis for determining hazardous thresholds of chemical pollutants in the environment, and correspondingly for determining hygienic standards. Synergistic and cumulative effects of pollutants are also considered.

In solving questions concerning a comprehensive toxicological limitation (hygienic standards) of chemical compounds in the environment, prime attention is devoted to threshold and safety levels of toxins that enter the organism separately. These levels may be established, proceeding from the knowledge about the stages of chronic intoxication, which is an interaction of the processes of physiological adaptation and compensation of pathological phenomena (so-called "acclimatization") with a transition to decompensation. Difficulties are encountered when differentiating ordinary reactions of adaptation, including orientating reactions, which cannot be considered injurious, from pathological reactions (temporary sub-clinical, compensated).

In order to determine the borderlines of genuine adaptation, the following laws of biology were suggested:

- the law of unity of the organism and environment,
- the law on unity of the organism as a biological system,
- the law on permanent numerity of a species, and

other laws, (I.V. Sanotsky, N.G. Ivanov, N.M. Karamzina, V.N. Fomenko [10]).

The first presumes determining stability of organisms subjected to chemical action, to additional physiological and extreme stresses. The use of different pharmacological functional tests, as well as physical stresses (cooling, according to restoration of rectal temperature test; ionizing radiation - according to lethality and others) has made it possible to classify the state of genuine adaptation or subclinical pathology under the action of small doses and concentrations of mercury, lead, CCl_4, benzene, dimethylformamide, pyridine, carbon disulfide, triphthazine and many other compounds.

The *second* presumes a comprehensive study of the organism since one or several indices may be interpreted erroneously. For instance, the "acclimatization" to many irritant toxins was proven to be the phase of chronic intoxication. Adaptation to certain mutagenic (ethers of trichlorphenoxyacidic acid) aberration test of chromosome of the bone marrow cell is accompanied by a rise in chromosome aberrations in the cells of the liver.

The *third* - the permanent numerity of a species is connected with the action of a substances on the reproduction processes. A study of the selectivity and active thresholds for several dozen substances has made it possible to establish that comparatively few substances have specific gonadotrophic, embryotrophic, mutagenic properties, namely - chloroprene, ethylenimine, urethane, ethyline oxide and others.

The criteria of hazardness should be the deviations of the indices beyond the limits of normal physiological fluctuations (2σ from the mean or average seasonal values), but not yet obvious signs of pathology.

The metabolical criteria of hazardous action many be the following criteria:

- the level of action at which semi-ejection of the toxin from the organism increases as compared with lower levels of action (I.V. Sanotsky),

- the level of action at which the activity of enzymes is suppressed (2σ from the mean or average seasonal fluctuations); the effect is aggravated when there is a specific pharmacological stress on the enzyme (V.V. Kustov, L.A. Tiunov [13]).

The above-mentioned methods may be regarded as a methodological basis for determining *hazardous* thresholds of chemical pollutants in the environment, and correspondingly, for determining hygienic standards.

The safety levels of action in case of separate entry of substances of separate environments must take into consideration remote effects - such as gonadotrophic, embryotropic, mutagenic, blastomogenic, arteriosclerotic action and other effects. In this problem, in spite of certain headway that has been made, there are still many unsolved questions, in particular, extrapolation to human beings of data obtained from experiments involving animals, and others.

Upon simultaneous entry of chemical substances through the gastro-intestinal tract and the respiratory organs, most frequently there is a summation of effects at the MPC or chronic action threshold levels, (S.M. Pavlenko [8]). The calculations by E.I. Spinu [11] indicate that the quantity of pesticides entering the organism through the environment at MPC level for each environment, when summed up exceeds the harmless dosage. It has been proposed to establish a harmless maximum permissable dose of a preparation for man, obtained as a result of summing up the maximum permissable doses and concentrations in all environments with consideration for the share of each environment. In order to calculate the maximum harmless dose during simultaneous entry of the substance from different environments, it has been proposed to use the principle of hygienic standardization that is employed at the present time in respect to combined entry of substance with the same action, proceeding from the additive effect (A.I. Korbakova, N.I. Shumskaya [4]).

Certain difficulties are encountered when involved in comprehensive hygienic standardization in view of significant differences in the toxicity and nature of the action in respect to certain substances when toxins enter through different channels: nitryl fluoride (Yu.N. Korshunov [5]), bromium (A.M. Klyachkina [6], O.A. Krylov [12]).

In natural conditions, when these substances are inhaled or enter through the gastro-intestinal tract, there is a considerable difference in the regimes of action by these chemical compounds. It has been established that the intermittant regime of action in certain cases proves to be obesity or adipsia and inanition. During the development of such a malfunction, the sole index of regulatory impairment might be a certain finickiness about food, such as exaggerated responses to the tastes of quinine (bitter) and saccharin (sweet). We are examining methylmercury for such effects in mice.

3. Specific Functions

A chemical would be explored during phase 2 only if it seemed capable of conferring some especially useful benefits. An assessment in depth requires a substantial investment in time, talent, and money. Sometimes, of course, such an assessment is inescapable, as in the case of methylmercury, because it is so pervasive in food.

3.1 Sensory Function

Research on problems of what has been called *animal psychophysics* [6] is flourishing, taking advantage of progress both in operant behavior and in technologies such as the digital computer. These developments offer toxicology an important tool for gauging impairment in sensory systems, which, for some classes of substances, are primary targets.

A cogent example of the utility of animal psychophysics is provided by work performed by Dr. Hugh Evans in our laboratory. Methylmercury, at least in primates, appears to concentrate in those areas of the cerebral cortex that subserve vision. Not only is tissue destruction visible in this area, but poisoned humans experience constriction of the visual field.

Starting with the knowledge that ablation of visual cortex impairs discrimination of form more than simple discrimination of brightness, we decided to approach the assessment of visual function by training monkeys to distinguish among different geometric shapes. We also reasoned that the constricted visual fields might simply be due to the poorer representation of the peripheral visual field on the cortex (as well as in the distribution of retinal receptors). If this were the case, reducing the number of receptors stimulated, especially the rods in the peripheral field, should exaggerate whatever impairment is present. This parameter was investigated by varying the luminance of the stimuli from easily visible at ordinary room illumination to barely detectable after 10 minutes of dark adaptation.

Figure 2 shows the arrangement devised for this experiment. The

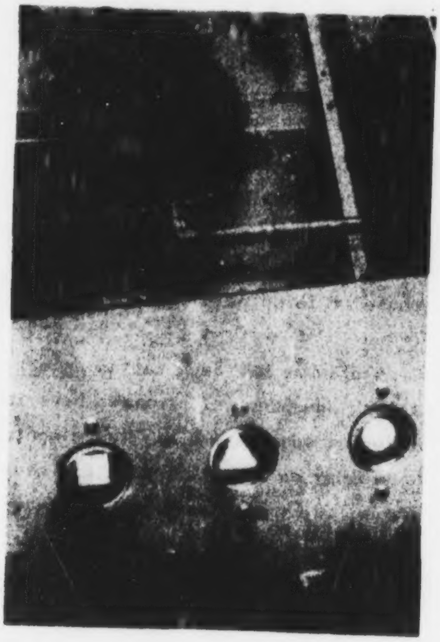


Figure 2. Arrangement for testing visual discrimination in monkeys. A mirror was used to show both front and rear views. A small quantity of fruit drink is delivered through the brass pipe if the monkey presses the key with the square.

monkey presses the key on which the square is projected in order to obtain a juice reward. Incorrect responses are followed by a period during which no events are programmed. All of these events are controlled and recorded by an on-line digital computer. Computer technology is used throughout our laboratory for these purposes; we believe that precise exposures and biochemical analyses should not be hampered by crude behavioral analyses. (See Weiss [7] for a survey of applications.)

The history of one monkey (M. speciosa) exposed to methylmercury appears in Figure 3. The uppermost panel represents the brightest luminance. The lowest panel shows accuracy at the dimmest luminance.

After 4 priming doses of methylmercury chloride, the monkey's whole blood level of methylmercury was maintained at about 2500 ppb by weekly oral doses of 0.5 mg/kg. After approximately 10 weeks, performance at the lowest level began to deteriorate, was partially regained for a few weeks, then finally deteriorated quite badly. At the same time, the monkey was able to maintain virtually perfect accuracy at the higher luminances until about the 30th week, when the monkey was virtually blind.

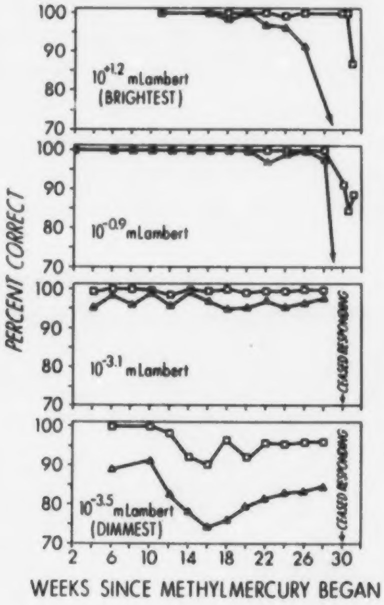


Figure 3. Deterioration of visual performance in a monkey treated chronically with methylmercury.

Similar techniques have been used in other modalities. Stebbins [8], for example, has shown that ototoxic antibiotics can be detected by training monkeys, in essence, to trace their audiograms.

3.2 Motor Control

Animals can be trained to make many different varieties of motor responses, some of rather awesome complexity. Since behavior basically comprises an organism producing changes in its environment by various muscular movements, evaluations of motor performance should play a major role in detailed studies of toxic effects.

An example of how one might pursue such questions is illustrated in Figure 4. The picture shows a squirrel monkey (S. sciureus) inserting its paw into a slot that contains a lucite plate mounted on a strain gauge. The monkey was trained to press the plate with a force between 5 and 15 grams in order to obtain a 90 mg sucrose pellet from the feeding magazine on the right. Using such a paradigm, it becomes possible to measure variables such as proportion of response time spent within the specified limits, the number of excursions above and below the limits, and other indices of precision of motor control [9, 10]. A digital computer controlled the experiment and was used for analysis.

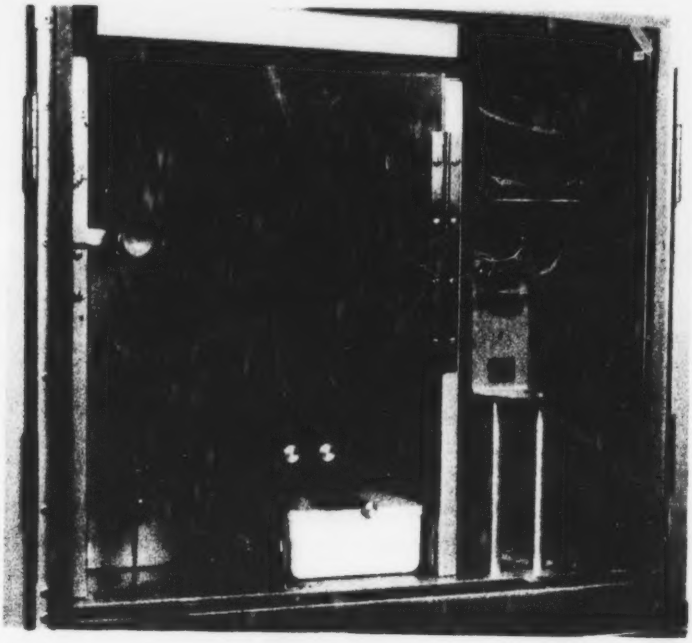


Figure 4. Arrangement to assess fine motor control. The monkey inserts its paw into the slot and is reinforced with a sucrose pellet if it maintains a force of 5 to 15 grams for 2 consecutive seconds.

Figure 5 comes from an experiment whose aim was to study the onset of motor incoordination after weekly doses of methylmercury chloride. What can be observed on the figure is an acute disruption of performance soon after the weekly oral doses plus a gradual deterioration through the total period of exposure. This deterioration was manifested as a high initial force, then a gradual slide into the designated range instead of the precise entrance into the band characteristic of baseline performance.

One can use similar reinforcement contingencies to measure strength. A recent publication by Dews and Herd [11] examined the effects of ganglionic blockers on the pressor responses induced by muscular contraction. The situation employed monkeys (M. mulatta) trained to pull a weighted rod for a food reinforcement. In our laboratory, to examine

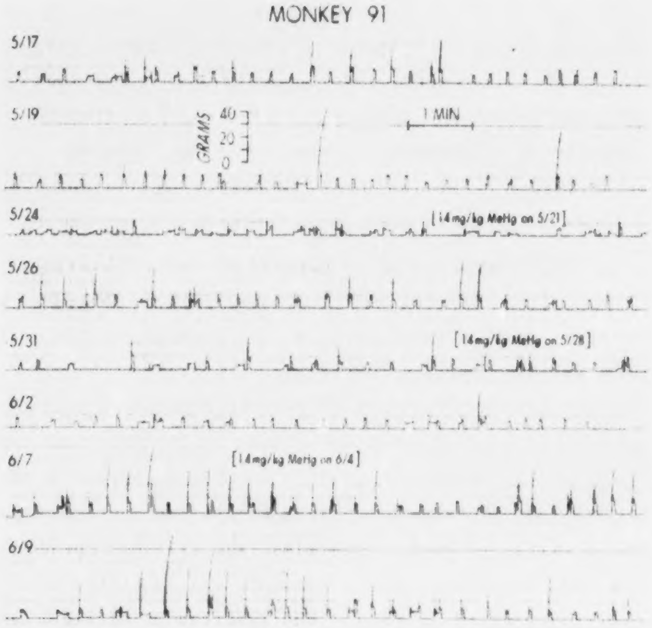


Figure 5. Changes in the ability of a methylmercury-treated monkey to exert a relatively constant force. Note how the first dose (5/21) produced an acute effect on 5/24. Deterioration of performance on 6/7 and 6/9 was marked by inability to come directly into the proper range (cf., 5/17 and 5/19).

static strength, we have trained squirrel monkeys to maintain forces of over 200 grams in order to avoid an electric shock to the tail.

3.3 Complex Processes

Many human activities, and many toxic phenomena, involve not pure sensory or motor function, but responses to complex relationships in the environment. Some of these may be approached by examining an organism's behavior in the context of what we call "Schedules of Reinforcement"; that is, how the properties of behavior are governed by specified relationships between behavior and its consequences. The advantages of such an approach lie in the large number of variations an experimenter can explore using the same basic technique. It has proved immensely useful to behavioral pharmacology, and I predict that behavioral toxicology will see its repertoire of methods enhanced in the same way.

One current project in our laboratory, carried out by Dr. Tina Levine, is directed toward the behavioral effects of carbon disulfide, partly because of its interesting neuropharmacologic properties: it appears to act as a dopamine-β-hydroxylase inhibitor, so that it retards the conversion of dopamine to norepinephrine. Pigeons are the first species we turned to because they are easy to handle and train.

Figure 6 shows how some of our pigeon chambers are constructed. The pigeons, usually maintained at 80 percent of their free-feeding body weight, are trained to peck an illuminated disk connected to a switch. When the pigeon is reinforced, a food magazine, loaded with grain, is elevated into position for eating.

Figure 7 shows how one can quantify certain effects of carbon disulfide exposure. The pigeons whose records appear here were tested in a slightly different chamber--one with two pecking keys. If the pigeon pecked the left key 8 or more times before pecking the right key, it received access to food. Otherwise, the left key counter was reset. Laties [12] found that such a schedule was sensitive in different ways to a variety of drugs. The tracings in Figure 7 demonstrate that with increasingly longer exposures to carbon disulfide the rate of responding decreased, but at no sacrifice in accuracy. The levels required to produce such an effect are rather high compared to

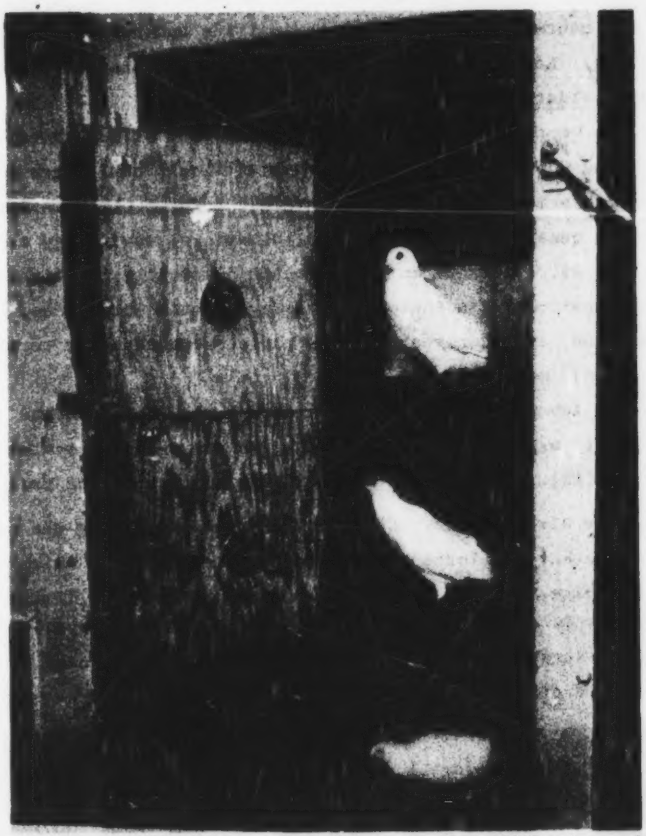


Figure 6. **Pigeon test chambers. The pigeon in the middle is pecking at the response key. The pigeon at the bottom is eating from the food magazine.**

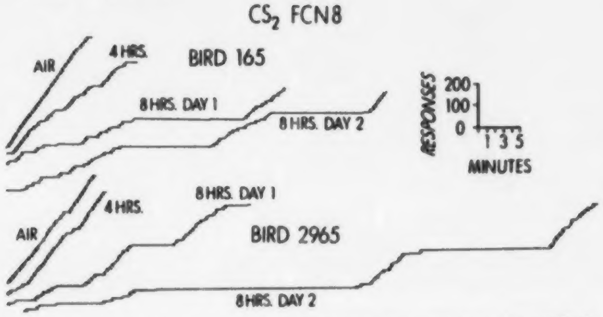


Figure 7. Changes in rate of pecking induced by carbon disulfide exposure. The records are cumulative; each response produces an increment in height, so that, with the recording paper moving at constant speed, slope is equivalent to response rate. The slashes on the record indicate reinforcements. The pigeons were removed from the exposure chambers for testing.

the TLV for humans, but we currently are more interested in the relation between the neurochemistry of carbon disulfide and behavior than in standard setting. Later, we will be asking such questions of primates.

4. Human Evaluations

Although we all recognize that the assessment of health effects in exposed human populations poses the most difficult challenges to environmental health science, the problems are not insurmountable. Particularly for specific questions about function, behavioral toxicology can draw on many decades of refinement in experimental psychology for techniques to determine impairments in sensory and discriminative processes, complex motor function, and phenomena such as those subsumed under terms like "learning" and "memory."

When our laboratory needed to evaluate three women who had been occupationally exposed to mercury vapor, we arranged the system shown in Figure 8 [13]. The patient kept her finger in a lucite trough attached to a strain gauge. Lights on a small box facing the patient indicated whether the force exerted on the strain gauge, which is an isometric device, was above, below, or within prescribed limits. (Note how this task is analogous to the one used with the monkeys.) We wished to obtain measures of motor function that not only reflected overt tremor, but that could give us an indication of fine control.

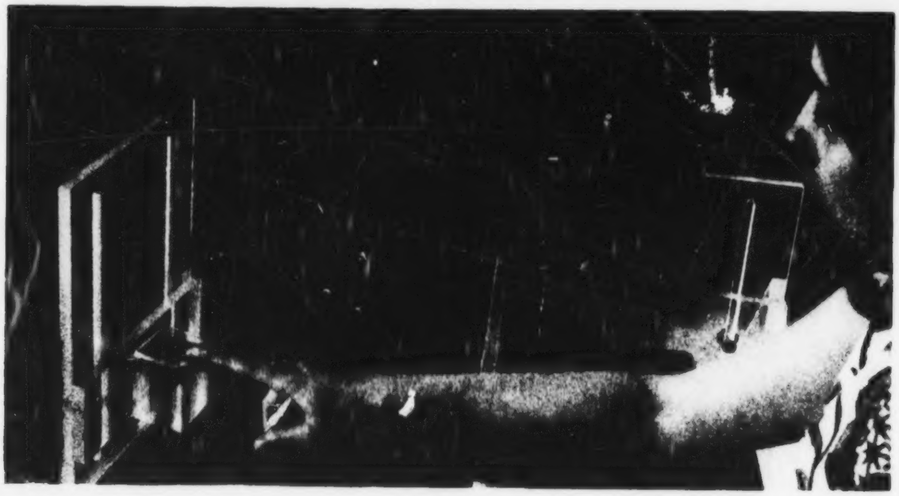


Figure 8. Device for measuring fine motor control in humans. The lucite trough is connected to a strain gauge. The indicator lights denote "start," "above" and "below."

usefulness of some of the more subtle methods of investigation. We may register effects of carbon monoxide which are equivalent to the effect of a cup of coffee or tea or the intake of a small amount of alcohol. The practical importance of such investigations is limited.

WEISS (U.S.A.)

We must not forget that the society, and the public agencies that represent it, must determine what are "small" effects. Remember that the CO literature is based on young, healtny men; and we know that older people are more susceptible.

Furthermore, CO is only one constituent of a chemical soup in which we live. The ingredients interact - may have additive, or synergistic properties. CO may at times, simply be the additional load that breaks beyond the threshold.

NEEDLEMAN (U.S.A.)

1. Would you extend your comments on the discriminating power of a neurological examination to the sensitivity of health questionnaires of routine clinical examinations?

2. Could you put your remarks into a developmental context? That is, what are the possible effects of such interferences in perceptual, motor or cognitive processes on a growing child's brain, during critical periods of neurogenesis, myclogenesis, or other forms of maturation and learning?

WEISS (U.S.A.)

1. Routine clinical examinations are not meant to detect subtle functional impairment. They are designed to elicit indications of frank disease. Even the addition of a skilled neurological examination may not be enough to distinguish phenomena that might only be expressed as vague, subjective complaints, or complex malfunctions discerned only with advanced technology.

2. The developing nervous system is especially susceptible to toxic processes. As I pointed out in a recent article in *Pediatrics*, some of these effects are less important in themselves than in what they portend. Experiments on prenatal exposure to methylmercury indicate that many such consequences may be revealed only in advance age, when other processes also contribute their effects.

2435

SCHLUßSITZUNG

CLOSING SESSION

SEANCE DE CLOTURE

SESSIONE FINALE

SLOTZITTING

Preceding page blank

CONCLUSIONS ET REFLEXIONS DES CONSEILLERS SCIENTIFIQUES

Présentées par

le Prof. A. LAFONTAINE
Belgique

En matière de protection de l'homme et de l'environnement, les critères sont définis comme un jugement, basé sur des données scientifiques traduisant une relation, autant que possible exprimée numériquement, entre l'exposition d'une cible à un facteur d'agression et le risque et/ou l'effet défavorable ou indésirable au niveau de cette cible: l'établissement de critères est la première des démarches qui, en logique cartésienne, doit aboutir d'abord à la fixation d'objectifs de qualité, ensuite à l'établissement de normes, de règles et de codes de bonne pratique.

La santé de l'homme et de son espèce étant sans conteste la plus importante des préoccupations, il était logique que les trois organisations responsables du Symposium aient eu pour premier souci de réunir les connaissances scientifiques existantes pour progresser dans l'établissement des relations entre l'exposition aux polluants et les effets directs et indirects sur la santé, afin d'arriver à une évaluation aussi rationnelle que possible des risques, et, dans un stade ultérieur, pour décider des programmes d'intervention et des actions en vue de prévenir ou réduire la pollution ou d'en limiter les répercussions.

L'expérience ayant hélas, montré combien souvent fragmentaires étaient les informations et combien peu exploitables étaient de nombreuses études expérimentales et certaines études épidémiologiques, les promoteurs se rendaient parfaitement compte des difficultés qui se présenteraient, d'autant plus que certains facteurs moins pertinents risquent de s'intriquer aux aspects strictement scientifiques. Ils savaient aussi que beaucoup de recherches avaient été conduites pour des raisons différentes de celles de la poursuite de l'établissement de critères. Aussi, en plus des nouvelles données qui pourraient être recueillies, avaient-ils pour but:

a) d'établir une meilleure planification, une motivation plus spécifique et une orientation plus efficace et rigoureusement objective des recherches;
b) de découvrir la nature et l'importance des lacunes:
c) d'identifier, autant que possible, les secteurs où des réalisations sont impératives en raison de l'urgence ou de la priorité des problèmes et ceux pour lesquels les données existantes, même si elles sont encore incomplètes, sont suffisantes et valables pour passer à l'action.

Preceding page blank

Malgré les difficultés, malgré le caractère inégal et parfois dispersé des communications présentées, les conseillers scientifiques estiment néanmoins le bilan comme largement positif, si l'on considère les divers objectifs envisagés.

Une série de données nouvelles ont été apportées concernant entr'autres la pollution atmosphérique urbaine, les dangers des métaux lourds, les nuisances acoustiques, les techniques expérimentales, les indicateurs d'exposition, les mesures au niveau biologique, les nouvelles approches expérimentales des phénomènes du comportement. Des nouveaux problèmes ont été abordés tels ceux posés par les biphényls polychlorés ou le chlorure de vinyle. Mais davantage se sont précisées les données scientifiques requises pour la prise de décision pour la protection de la santé et ont été identifiées les lacunes fondamentales dans les connaissances, les orientations futures des recherches et des terrains à explorer, pour arriver à des bases scientifiques nécessaires pour les processus de réflexion et de décision.

Nous manquerions toutefois d'objectivité si avant de préciser certaines réflexions et suggestions, nous ne soulignions pas certaines faiblesses démontrées par les documents présentés. Par exemple, l'engouement trop unilatéral pour certains thèmes comme les métaux lourds ou pour certains secteurs comme les polluants atmosphériques. Les causes en sont probablement les suivantes: enthousiasme ou facilité scientifique, orientation politique, pression du public. Par contre, d'autres thèmes ont attiré peu l'attention comme les dérivés nitrés, les nitrosamines, les mycotoxines ou le manganèse. Bien qu'ils ne manquent pas d'actualité, certains secteurs comme ceux des résidus solides et de la contamination du sol n'ont pas préoccupé les auteurs, et la toxicologie des eaux destinées à la consommation humaine pourrait paraître aujourd'hui pour un auditeur non averti, comme un problème résolu. D'autres secteurs comme celui des médicaments ou des additifs alimentaires ou certaines nuisances comme celles liées aux radiations ionisantes et non ionisantes n'ont pas été considérés au cours de ce Symposium: les raisons majeures sont liées à des cloisonnements devenus traditionnels mais qui mériteraient d'être levés en vue d'une approche plus globale des problèmes, la cible de ces diverses nuisances étant la même, l'homme et son espèce.

Par ailleurs, si les Conseillers Scientifiques regrettent une dispersion parfois exagérée des problèmes de la santé de l'environnement au niveau d'un nombre considérable d'organismes, ils tiennent au contraire à souligner la coopération qui s'est établie entre les trois organisations responsables du Symposium et à les remercier pour l'opportunité exceptionnelle qui a été donnée à des chercheurs européens et américains et par la liaison de l'O.M.S., et à des chercheurs du mond entier, de se rencontrer pour chercher à établir des critères de santé (les critères restent en dehors de toute considération socio-économique ou politique) communs à tous les hommes de cette "seule terre" et pour oeuvrer de manière aussi coordonnée et fraternelle que possible.

Parmi les nombreuses réflexions qui suggèrent les débats du Symposium, nous pensons utile de retenir, outre la mise à exécution des programmes d'action concernant la liste présentée par l'O.M.S. de substances pour lesquelles des informations doivent être assemblées et des recherches poursuivies, quelques propositions particulières:

1. Avant tout, il importe de s'exprimer clairement et la nécessité d'un *glossaire* définissant le sens des termes utilisés en matière d'environnement s'est confirmée.

2. Trop souvent, on considère indépendamment chaque polluant et chaque secteur en oubliant que l'homme joue un rôle *d'intégrateur des nuisances*: un même toxique peut l'atteindre par diverses voies et divers agents altéragènes, y compris ceux liés à certaines habitudes (usage du tabac par exemple), peuvent toucher le même organe cible. Les risques liés aux polluants chimiques et physiques ne doivent pas faire oublier les risques biologiques et microbiologiques. La notion de charge corporelle, d'incorporation totale doit se généraliser de même que celle des doses admissibles par jour, semaine, mois ou année, suivant le cas,

De plus, à la notion de concentrations dans l'atmosphère, dans l'eau ou dans le sol, doit s'ajouter celle de la capacité toxicologique d'un milieu, d'une région, d'un bassin, en particulier pour les substances non dégradables: il s'agit de la quantité totale de substances polluantes que peut supporter sans dommages intolérables ce milieu, cette région, ce bassin.

3. Les débats ont souligné le besoin de développements méthodologiques, notamment en ce qui concerne l'épidémiologie, les modèles animaux, le prétesting et les balances avantages/desavantages:

a) *les techniques épidémiologiques sont fondamentales*, non seulement pour évaluer l'influence directe ou indirecte des pollutions sur la santé, mais aussi pour identifier de nouveaux risques ou inconvénients et pour apprécier l'efficacité des actions entreprises. L'epidémiologie devrait pouvoir s'appuyer davantage sur les informations apportées par un public prévenu et formé et par un corps de médecins praticiens avertis: la clinique générale et les observations en milieu professionnel pouvant être d'une importance capitale, même si cela demande une préparation du corps médical. La mise en oeuvre de programmes épidémiologiques plurinationaux peut être très utile pour évaluer l'effet concomitant d'autres facteurs comme les conditions d'ambiance ou les influences géographiques, climatiques, etc.

b) le développement, au plan des essais toxicologiques, de modèles animaux pour les maladies humaines est indispensable pour mieux comprendre les effets observés et pour assurer le maximum d'efficacité à l'examen préabable des nouveaux produits et des nouvelles technologies. Ces modèles devront être conçus de manière à serrer au plus près les études épidémiologiques;

c) le problème du "pretesting" doit être un souci majeur des scientifiques: il importe, sous peine d'exposer l'humanité à des risques imprévisibles, que les nouveaux produits chimiques, les nouveaux procédés et les nouvelles sources d'énergie soient, préalablement à leur emploi étendu, l'objet d'une évaluation aussi large que possible sur la nature et l'importance des risques à court, moyen et long termes y compris la recherche des effets mutagènes, cancérogènes et tératogènes éventuels et de l'établissement d'une balance avantages/désavantages pour l'homme et son espèce. Un mécanisme méthodologique doit être élaboré qui tente de prévoir au mieux les risques toxicologiques et écologiques divers mais prévoie également les critères de pureté applicables, le sort dans l'environnement des substances mises en oeuvre et leur détection (du produit pur, ainsi que des impuretés et métabolites éventuels) dans les différents composants du milieu;

d) une balance entre les avantages et les désavantages pour la santé des produits et techniques mis en oeuvre pour l'homme est indispensable: toutefois, les approches actuelles sont souvent inadéquates, sur le plan conceptuel comme sur le plan technique et il importe de repenser le problème de manière multidisciplinaire. Dans un même ordre d'idées, il importe de mieux évaluer le coût de la pollution et de la lutte contre les polluants ainsi que l'efficacité des moyens de lutte et de leurs effets secondaires éventuels sur le plan de la santé. Ces notions seront utiles à côté d'autres éléments socio-économiques et régionaux dans le processus de décision partant des critères et allant vers les objectifs de qualité et les normes.

A ce dernier point de vue, une attention particulière devrait être accordée aux problèmes qui se posent pour les pays en voie de développement: il pourrait arriver que les besoins en développement l'emportent en urgence sur les exigences de la protection.

4. On observe souvent à côté de manifestations franches ou du moins assez aisément identifiables des changements considérés comme infra-pathologiques ou d'interprétation difficile comme la stimulation des enzymes mitochondriales ou la modification de la déhydratase de l'acid delta aminolévulinique chez les personnes exposées au plomb. Des recherches doivent permettre de donner un sens plus précis à ces modifications et de savoir s'il s'agit de simples concomitants ou d'altérations subtiles précédant des manifestations pathologiques: en même temps, il serait utile de savoir si ces modifications peuvent être employées comme des indicateurs d'exposition.

5. En relation avec le point précédent, se soulèvent des problèmes:

a) le choix des groupes critiques à prendre en considération au point de vue de la santé et de l'ampleur des risques éventuels qui pourraient être raisonnablement acceptables pour ces groupes;

b) le choix des priorités en matière de recherche scientifique basées notamment sur les connaissances sur la nature du risque, son ampleur, sa réversibilité et sur les possibilités d'action, qu'il s'agisse de polluants naturels ou provenant de l'activité humaine.

6. De même, il importe de considérer différemment les risques observés dans les conditions habituelles et les risques accidentels: les limites acceptables dans ce dernier cas seront dérivées de critères appliqués à l'exposition aiguë et les mesures d'intervention appropriées à l'ampleur du risque et du nombre d'individus menacés.

7. En ce qui concerne les valeurs actuellement admises comme normes, il est sûr que certaines d'entre elles à la lumière des connaissances acquises, doivent être revues: c'est particulièrement le cas de certaines concentrations maximales admissibles dans les milieux de travail. En effet, certains effets à long terme n'ont pas été suffisamment pris en considération parce qu'on n'a peut être pas tenu assez compte du fait que des exposition non professionnelles viendraient s'ajouter à des exposition professionnelles et sur tout parce qu'on a parfois un peu perdu de vue que des femmes en état de procréer travaillent de plus en plus dans l'industrie: certaines valeurs doivent indiscutablement être repensées en tenant compte du transfert transplacentaire et transmammaire et de la protection de foetus et du nourrisson.

Nous avons défini le terme critère au début de cet exposé. Nous voudrions, avant d'envisager certaines études fondamentales dont l'intérêt est apparu au cours des débats, attirer l'attention de nos collègues sur trois points qui nous paraissent importants:

1. D'abord, certains effets apparaissent plutôt comme des désagréments comme les odeurs ou certains inconvénients acoustiques; il n'est pas toutefois possible de chiffrer l'exposition ni de quantifier les effets et pourtant un jugement critérial est généralement possible, qui permettrait la mise en marche du processus décisionnel: cela ne veut pas dire qu'un effort technique et méthodologique ne doit pas être fait pour arriver le plus tôt possible à des expressions numériques.

2. Il est important de souligner par ailleurs que des décisions doivent être prises dans certains cas quant à la fixation de normes ou de valeurs de référence ou à la prescription de mesures réglementaires avant que les critères n'aient pu être

élaborés; il importe dans ce cas de réunir le maximum de données scientifiques, même partielles ou analogiques, à la condition qu'elles soient suffisamment évidentes pour étayer ces décisions. Elles doivent susciter le plus tôt possible des confirmations expérimentales ou épidémiologiques.

3. Enfin, il importe de poursuivre, des recherches sur le plan expérimental et clinique pour mieux évaluer par exemple les effets psychologiques de certaines nuisances ou de certains stresses de l'existence moderne et mieux connaître les effets psychologiques de certaines nuisances (comme les équivalents biologiques du bruit).

Enfin, parmi les recherches fondamentales d'appui nécessaires que ce Symposium a permis d'identifier, nous retiendrons particulièrement les points suivants:

1. l'étude des facteurs d'agression, qu'ils soient d'origine naturelle ou apportés par les activités humaines doit être approfondie, quant à leur mécanisme d'action, quant à leurs interactions au niveau du milieu et des cibles;
2. une attention plus approfondie doit être accordée aux effets sur le potentiel génétique, sur l'organisme foetal (même s'ils sont très tardifs et n'apparaissent que lorsque le jeune être est arrivé à l'âge adulte), sur les transferts transplacentaires et transmammaires;
3. les transformations métaboliques des substances xénobiotiques dans le milieu, le long des cycles biologiques et au niveau de l'organisme humain n'ont pas toujours été suffisamment pris en considération: des recherches expérimentales dans ce sens sont indispensables;
4. de nouvelles recherches sont indispensables en ce qui concerne l'existence ou l'absence de seuil pour les effets cancérogènes: les mécanismes de réparation, prouvés par la biologie moléculaire, oblige à repenser cette notion;
5. par ailleurs, n'existe-t-il pas à l'égard de certains facteurs d'agression des mécanismes d'adaptation ou de compensation autres que la sélection naturelle et qui se sont manifestés au cours de l'histoire humaine? Ils mériteraient d'être identifiés, étudiés et évalués;
6. tout en écartant des préoccupations actuelles les critères écologiques, il importe toutefois d'identifier et d'évaluer les effets indirects sur la santé de l'homme des effets écologiques comme l'atteinte de certains végétaux essentiels à la survie de l'homme ou comme la pollution thermique avec ses retentissements sur l'environnement et entr'autres sur le plan microbiologique et parasitaire;

Among the fundamental back-up research which this symposium has shown to be necessary, we would lay particular emphasis on the following points:

1. the study of agressive factors, whether of natural origin or derived from human activity, must be extended, with respect to the manner in which they act and their interactions in the environment and in the targets;

2. greater attention must be paid to the effects on genetic potential, on the foetal organism (even if they are very slow-acting and do not appear until adult age) and on transplacental and transmammary transfers;

3. the metabolic transformations of xenobiotic substances in the environment, throughout the biological cycles and at the level of the human organism have not always been sufficiently taken into consideration, and experimental research into these is essential;

4. research must also be undertaken into the question of whether a threshold for carcinogenic effects does or does not exist: the existence of repair mechanisms, proven by molecular biology, demands that this concept be considered a fresh,

5. furthermore, have not adaptation or compensation mechanisms other than natural selection appeared with regard to certain agressive factors during the course of human history? These should be identified, analysed and appraised;

6. while excluding ecological criteria from our current preoccupations, it is nevertheless important for us to identify and assess the indirect effects on human health of-adverse ecological influences affecting, for example, certain plants essential to human survival, or thermal pollution, with its repercussions on the environment and, amongst other things, on microbiological and parasite life;

7. current monitoring techniques are sometimes cumbersome; they must be better adapted to the numerical evaluation of exposure and new and if possible polyvalent indicators of pollution in the environment and in man must be sought in order to facilitate and increase the effectiveness of epidemiological surveys;

8. among long-term effects, the phenomenon of acceleration of physical and mental ageing has not been sufficiently taken into consideration, nor have, perhaps, certain unforeseen repercussions on ontogeny; a fundamental approach is desirable as well as guided epidemiological surveys;

9. although prevention is admittedly better than cure, and it is better to avoid than to combat pollution, nevertheless it may be extremely profitable to search for countermeasures and remedies at the biological and physiological level to certain kinds of contamination, all the more so since some of them, being of natural origin, are inevitable.

In conclusion, I would like to stress, on befalf of my colleagues and those whom we wish to protect, the importance of centripetal information flow, on the one hand, and of setting up a data bank on the other hand. Too many data, available in the fields of industry or agriculture or of preventive of occupational medicine for various reasons fail to reach those responsible for epidemiological surveys. Moreover, the practising doctor, perhaps because he is not sufficiently prepared, neglects to communicate information which could often be invaluable; his attention should be drawn in particular to the observation of high-risk groups and to the usefulness of biolocical monitoring. Let us hope that this appeal will suffice and that a favourable response will make it unnecessary to lay down rules for the transmission of this information.

Similarly, the setting up of a toxicological data bank by the random sampling of suspicious coincidences seem essential to us, and should go hand-in-hand with regular surveillance of population samples, either representative or corresponding to particularly sensitive groups. A data bank of this type would be of immense value to WHO and would constitute a vital foundation for the epidemiological surveys which we are proposing.

Let us hope that the efforts made on both sides of the Atlantic will be united and concentrated in this direction and that this will prove to be one of the concrete achievements of this symposium, which was made possible only thanks to the very close collaboration of the three organizations concerned and the unflagging energy of the organizers.

CLOSING SPEECH

DR. B.H. DIETERICH
Director Division of Environmental Health
World Health Organization

In the few minutes available for my statement, I want to tell you how we of WHO appraise and will be able to make use of the material presented during this symposium and of the many interesting discussions that took place. We have been pleased to co-sponsor this symposium for two particular reasons, namely:

1) To help provide the widest possible forum where scientists from all countries could freely exchange their experiences, and

2) To demonstrate how a national regulatory agency, an international health agency and a regional economic community can approach problems of environmental health together.

I will present my reviews as replies to two questions:

1) How will we be able to use the specific information presented?

We have obtained a great deal of specific information on methodology. Most important in this connection is perhaps the information presented on the design of population studies taking into account the need for a multi-factorial approach. We are interested in promoting methodology which will enable scientists in various countries to work together, and your papers have provided examples as to how this can be done.

We have learned on the one hand that some of the work done and some of the methods applied did not always produce results which could be related to the specific problems posed in environmental health, but on the other hand that you have made use of rational models in planning your scientific studies. This experience will contribute to our efforts to develop and promote agreement on methods for international comparative analysis of environmental health effects.

Still on methodology, interesting proposals have been made for the selection of meaningful parameters both for environmental conditions and for measuring human response. I believe that the symposium helped to promote agreement amongst scientists in respect of prediction models which might be applied in future scientific work and this too is of great interest to us.

There is no doubt that the symposium has confirmed the value of both toxicological and clinical and epidemiological methods as well as the limitations inherent in both of them. I believe that we will have to accept that the planning and implementation of meaningful population studies is a problem in itself, and that it would be false to expect immediate results which would help the legislator and administrator within just a few months in their respective tasks of setting and enforcing environmental standards. However, this should not discourage us, and I believe that we must continue to give a major role to human studies and we feel encouraged by the result of this symposium.

In this connection, we are grateful for the suggestions made to improve the monitoring of individual and population exposure and response for the elaboration of more meaningful statistical methods of analysis, for the suggestions which will help to plan and implement work in comparative toxicology and for the study of mechanisms of action and inter-action.

While the lessons learned with respect to methodology are important, I believe that the WHO Environmental Health Criteria Programme will greatly benefit from the data presented by you. This programme depends on research throughout the world, and I can state that the information presented during this week will broaden the scientific basis of this programme, particularly as regards the criteria documents which WHO has under preparation, such as for oxides of nitrogen, cadmium, lead, mercury, oxides of sulfur and resulting compounds, ozone and other oxidant and suspended particulate matter. The criteria documents on these substances are at various stages of development and in all the cases mentioned, I am sure that the specific data presented here will be of great help. This also applies to the papers on the effects of PCBs, and those on other persistent substances, fibrous dusts and the interaction studies on which some of you have been working. I should like to thank all of you for making this material available to us.

The results of this week's deliberations are also of specific interest in the promotion and planning of an increasing number of specific international case studies which we like to see organized wherever suitable occasions arise. Not only have we been able to learn more about a great number of new studies, but we were able to appreciate the fields of scientific interest and the scientific capacity of many people assembled here, with whom we were not acquainted in the past. I believe that this will help us in expanding contacts with the scientific community in making proposals for new programmes and priorities and in organizing more, and more meaningful, international comparative research.

2) Did the symposium validate the current approach to the assessment of environmental health factors and did it identify new directions which we should follow in the future?

While I would like to make a few remarks in reply to this question, I should first reiterate that we believe in (i) making scientific information an essential basis of administrative decisions at the national or regional level, and (ii) that administrative decisions are needed in the countries not only for the formulation and enforcement of national standards for environmental quality, but also for the allocation of more funds to environmental health research on a continuous basis.

Although I heard some pessimism, we have been reinforced in our belief that the assessment of environmental health effects of pollution and the presentation of information on dose/effect relationships in the form of international criteria documents are valid approaches and that they can be effective decision-making tools for use by legislators and administrators. In this connection, I would like to refer to a resolution adopted by the World Health Assembly in May 1974, in which WHO was requested to strengthen its efforts in the establishment and the promotion of international agreement on environmental health criteria.

Nevertheless, we acknowledge that for some time to come we will not be entirely successful in attempting to make regulatory action a fully rational process. Perhaps we must learn how best to support but not to replace and on a temporary basis, the scientific approach by prudent pragmatism in the planning and implementation of regulatory control. Although not too many suggestions have been made in this respect during the symposium, I believe that what has been said will help us to strenghten our contribution towards making health protection the ultimate objective of environmental protection.

Sure enough, our symposium did not make, nor was it intended to make, suggestions which would allow the application of principles of systems analysis to the planning of health oriented programmes of environmental pollution control. However, it provided a deeper insight into the environmental origin of some common chronic diseases, and it brought out the need to face the task of scientifically studying what might be the socially accepted risk of such diseases and the comparison of such risks with benefits derived from modern ways of life.

I believe we all should accept this challenge and undertake research in this respect. Perhaps this research will also provide further insight into the age-old question of the responsibility of the scientist who engages in creating new knowledge, which he must expect to lead to new hazards to public health.

I am not personally in favour of closing a meeting of this nature with a call for more support to research, but it appears that stronger financial and moral support is needed for environmental health effects research. One wonders whether some reallocation is not called for, keeping in mind the environmental origin of many of the chronic diseases for which massive research programmes are now under way.

The symposium also showed that we can still improve communication among us and particularly with the younger scientific generation, of whom we were pleased to meet so many during the symposium. We must also do more to explain science and scientific findings more effectively to the general public and to the decision makers. In planning future research we should accept the challenge expressed by one speaker during the early part of the symposium that apparently everybody does what everybody else does, but that nobody does what nobody else thinks about. Without making a case for exaggerated futurology, we have learned during this week that we must strengthen our efforts towards early identification of potentially new hazards to public health. This must become a continuing activity involving international collaboration, and I am sure that it will not only influence the planning of future research, but also the priorities which we have been following in the health assessment of the effects of environmental pollution.

Finally, on behalf of WHO, I would like to thank all those who have made this symposium what I consider a great success. This includes, first and foremost, those who have prepared the papers and have come here to present them, but also those who have spoken during the discussions. It includes our Secretary General, the Organizing Committee, the Scientific Secretariat, the Scientific Advisors, all of the conference staff, the interpreters and all those who have contributed to our work but have not been visible during the sessions. I would like to thank Unesco for making such beautiful facilities available to us and I would like to state that I personally consider it a great success and an encouragement for the future, that a national regulatory agency, a regional economic community and an international health agency have been able to organize a symposium in the spirit of mutual understanding and in pursuit of a common objective, namely to create an environment in which man can live and work and enjoy himself.

CLOSING SPEECH

A. C. TRAKOWSKI

Assistant Administrator for Research and Development
United States Environmental Protection Agency

I wish to express the gratitude of the United States Environmental Protection Agency (EPA) for the privilege of co-sponsoring and working with the World Health Organization and the Commission of the European Communities to organize and produce this stimulating scientific meeting. It has been a great effort by all concerned, from which we found a welcome and memorable diversion last Tuesday evening. The reception given by the Commission of the European Communities was a unique event at a unique place that will long remain a treasure in our memories, and we wish to most sincerely thank the Commission for its graciousness, its generosity and its hospitality. Also, we wish to extend deep appreciation to UNESCO for their provision of these facilities and staff support, without which this meeting could not have been as successful.

Hundreds of people have met here for five days to present and to learn of advancements in knowledge of the health effects of environmental pollution, and we have given plenary consideration to the problems of the use of scientific information in decisions to protect human health. Out of these presentations has come useful information in many disciplines and in many problem areas too diverse to be given comparative judgment or individual assessment here. However, in the totality of these presentations, I believe it is possible to observe certain trends and concepts in the pursuit of scientific knowledge on health effects caused by pollution and its application to pollution control. I would, therefore, like to put forth our observations in this regard, for whatever use they may be given as guides to further advancement toward the knowledge we are seeking.

First, we wish to note and to compliment the many contributors at this symposium on the interdisciplinary breadth and communication in their work. Indeed, we have seen during this week that the inter-disciplinary approach to investigations of health effects can succeed where single discipline studies have failed to reach desired research goals. We believe the advantages are apparent in dealing with the problems of health effects from pollutants, and we strongly urge intensification of the interdisciplinary approach.

Observation of the character of the progress reported at this symposium and of the methods by which this progress has been achieved suggests that, at the present time, there are limitations to the scientific basis for pollution control. Scientific methods are valuable for describing natural phenomena both qualitatively and quantitatively. In a time when man has been transported with exquisite precision from earth to the moon and back, it is difficult to believe that there are any problems that do not yield to scientific inquiry, or any decision not subject to rational, scientific information.

But, man's many-sided relationship to his environment must not be underestimated. Man is a complex and often inscrutable creature. He has created an intricate societal fabric that is now global in extent. This society, dependent on a precarious ecosphere, has become increasingly capable of exerting major influences on that ecosphere. The diverse problems already in our view appear to exceed our capability to solve them in a scientifically rigorous manner. We may reasonably question our abilities to solve even more complex environmental problems not yet suspected.

We probably possess the conceptual framework and techniques with which to develop solutions to these problems, given sufficient time and resources. But, faced with the urgency of self-evident needs for environmental control, we do not have the luxury of unlimited time. Additionally, research on environmental needs must compete with other strong requirements for limited resources. The interactions between environmental concerns and the complex, non-linear, social, political, economic, health and welfare aspects of human society must be pursued with imagination and unbiased dedication by scientists who have previously devoted themselves to more restricted fields and more classical methods. While they continue to direct their efforts toward the pursuit of scientifically substantiable information, they must also seek publicly acceptable methods for applying available, though inadequate, information to the decision-making processes which depend also on economic, political and geographical considerations.

We recognize that application of the results of scientific inquiry on the health effects of pollution may be limited in its usefulness at the present time, but we know no other way to acquire the needed information. What then, can we do, that the results of this symposium suggest, to improve our direction and techniques in our scientific pursuits.

We have seen increasing evidence to indicate that many environmental pollutants probably act differently in combination than they act separately. We know that urban environmental pollutants are rarely, if ever, present alone. Should we not, then, in order to devise an adequate control program, assess the effects associated with pollutants according to the way pollutants are actually found.

The need to use many synthetic industrial chemicals makes it essential to recognize and estimate the human and environmental hazards they pose and their societal acceptability with regard to the real or alleged matching benefits they confer. Hazards from a particular synthetic chemical,whether in consumer products or in the workplace, need not necessarily be accepted even when matching benefits appear high, as equally efficacious but nonhazardous alternatives are usually available. Imposition of a mandatory criterion of efficacy prior to the introduction of synthetic chemicals into commerce may well simplify such equations.

2. Cause For Concern

There is now little doubt that many diseases hitherto regarded as spontaneous, including cancer, birth defects and mental deficiency are caused by environmental pollutants. This realization is heightened by the exponential increase in human exposure to new synthetic chemicals --and their degradation and pyrolytic products in air, water and soil- which, in general, are inadequately characterized toxicologically and environmentally (Epstein [2]).

Recognition is now growing that the great majority of human cancers are probably due to chemical carcinogens in the general or working environments, and that they are hence ultimately preventable (Dunham & Bailar [3] ; Higginson [4]). There is also growing interest in the role of chemical carcinogens in activating oncogenic viruses. Epidemiological studies have revealed wide geographical variations in the incidence of cancer of various organs in the general population; in some instances these studies have incriminated local environmental pollutants.

The first evidence that environmental pollutants may influence the genetic constitution of future populations resulted some four decades ago from the discovery that high energy radiation induces mutations. The subsequent development of nuclear energy added a new dimension and enhanced awareness of the problem of genetic hazards. Safeguards have been accordingly developed to minimize radiation exposure. Once radiation-induced mutagenesis was discovered, there were reasons to suspect that some chemicals would act similarly, but proof of this was delayed until World War II when mustard gas was shown to induce mutations in fruit flies. Many and varied types of chemicals have subsequently been shown to be mutagenic. The likelihood that some highly mutagenic chemicals may come into wide use, or indeed may already be in wide use, is now causing serious concern. No nation has yet, however, promulgated regulatory requirements for mutagenicity testing.

There is also growing recognition of the importance of environmental pollutants in the causation of birth defects. National incidences of congenital malformations are unknown in the absence of comprehensive registries; it has been variously estimated as ranging from 3 to 4 percent of total live births. Three major categories of human teratogens have so far been identified: viral infections, X-irradiation and chemicals, such as mercurials and thalidomide. Although the teratogenicity of various chemicals had been experimentally recognized for several decades, it was only after the thalidomide disaster of 1962 that legislative requirements for three-generation reproductive tests were established.
A substantive body of data is now establishing clear relationships between exposure to a wide range of environmental and occupational pollutants and delayed neurotoxic effects, ranging from mild alterations in personality and behavior to advanced dementia. Illustrative, are the effects of lead, which at exposure levels and body burdens considered to be relatively low induce disturbances in personality and neuromuscular co-ordination in workers (Morgan & Repko [5]; Seppalaninen [6]) and hyperkinesis and learning disorders in young children (Environmental Protection Agency [7]).

3. Toxicity Testing

Pollutants to which humans are or may be exposed must be tested for acute and chronic toxicity *per se*, and also for the more specific effects of carcinogenicity, teratogenicity and mutagenicity. Toxicity testing must not be confined to the test agents *per se*, but should extend to their chemical and metabolic derivatives, pyrolytic and degradation products and contaminants. These considerations are further accentuated when the various derivatives or degradation products are of known toxicological or ecological consequence. Test agents must be administered acutely, subacutely and chronically to reflect the role of hepatic microsomal enzyme function in activation and detoxification. It may also be necessary to test for effects of concomitantly administered and otherwise nontoxic chemicals that may induce or inhibit microsomal enzyme function. Experiments must be designed to reflect the role of possible interactions between test agents -- administered by any route -- and between dietary factors and other chemicals, such as accidental and intentional food additives, drugs and air pollutants. Routes of test administration inter alia should reflect human exposure. While inhalation is the obvious route for testing of air pollutants, the importance of this route for other pollutants has been generally underestimated. Respiratory exposure is of particular human significance for pesticide aerosols and vapors, besides other aerosols. Surprisingly, there are virtually no data in the pesticide literature on chronic inhalation tests. Ideally and minimally, two mammalian species should be tested for toxicity per se, carcinogenicity, mutagenicity and teratogenicity. In certain circumstances when there is specific information that the rodent metabolism of the chemical pollutant in question is qualitatively markedly different from that in humans, other more appropriate species, such as pigs and subhuman primates, may also be tested. Reliance on small numbers of pigs or primates is no substitute for conventional rodent tests and may even mislead. In particular circumstances special considerations may dictate the use of less common species.

For carcinogenicity, teratogenicity and mutagenicity pollutants must be tested at higher levels than those of general human exposure; irrespective of route of administration, maximally tolerated doses are recommended for this purpose as the highest dose in dose-response studies. Testing at high doses is essential to the attempt to reduce the gross insensitivity imposed on animal tests by the small size of samples routinely tested, such as fifty or so rats or mice per dose level per chemical, compared with the millions of humans at presumptive risk. To illustrate, assume that man is as sensitive to a particular carcinogen or teratogen as the rat or mouse; assume further that this particular agent will produce cancer or teratogenic effects in 1/10,000 humans exposed. Then the chances of detecting this in groups of fifty rats or mice tested at ambient human exposure levels would be very low. Indeed, samples of 10,000 rats or mice would be required to yield one cancer or teratogenic event, over and above any spontaneous occurrences; for significance, perhaps 30,000 rodents would be needed (Epstein[2]). Of course, in any particular instance, humans may be less or more sensitive than rodents to the chemical in question; there is consequently no valid basis for the prediction of the relative sensitivities of test animals and man. Apart from the gross insensitivity of animal test systems and the impossibility of gauging human sensitivity from animal tests, ample data on interactions between carcinogens further confirm that it is not possible to predict safe levels of carcinogens based on an arbitrary fraction of the lowest effective animal dose in a particular experimental situation. Such considerations underlie the 1958 Delaney Amendment (P.L. 85-929) to the Federal Food, Drug and Cosmetic Act, which imposes zero tolerances for carcinogenic food additives. The amendment states: "...no additive shall be deemed to be safe if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal." The concept of zero exposure work standard has been accepted, but for only 14 occupational carcinogens, in regulations promulgated in the Federal Register on February 11, 1974. However, these regulations do not contain provisions to ensure effective implementation of the standards (Epstein [8]).

It must also be emphasized that testing at high dosages does not produce false positive carcinogenic results. There is no basis whatsoever for the frequent contention, particularly by industrial toxicologists and consultants, that all chemicals are carcinogenic, teratogenic, or mutagenic at high doses. To illustrate, in the recent Bionetics study, sponsored by the National Cancer Institute, about 140 pesticides were tested orally in mice of both sexes and strains at maximally tolerated doses from the first week of life until sacrifice at eighteen months; less than 10 percent of these pesticides were found to be carcinogenic (Innes et al [9]).

4. Monitoring and Epidemiological Surveillance

Persistent chemicals, chemical and metabolic derivatives of less persistent chemicals and their reaction and pyrolytic products should be detected and monitored in the environment - air, water, soil and food - and in body fluids or tissues of plants, animals and man. Selectively, only those chemicals or degradation products with known or presumed toxicological relevance should be monitored. Even with well-planned and well-executed toxicologic testing, it is likely that unexpected adverse effects from pollutants will occur, reflecting the insensitivity or inappropriateness of the test systems. Epidemiological surveys of human and animal populations may provide post hoc information on geographical or temporal clusters of unusual types or frequencies of adverse effects -- including cancer birth defects, and mutations -- after

ZIELHUIS (Netherlands)

I agree with many of the principles brought forward by the speaker. However, taking up some lines of reasoning yields consequences, I should like to question Professor Epstein about.

Traffic accidents constitute one of the most important public health problems. This could have been predicted from the start, even without animal experiments. According to Professor Epstein participation in automobile transport should be regarded as an amoral act, because non-driving human subjects are going to be killed or injured.

I agree that there are major defects in decision-making processes. One example: the very great attention paid to the toxicology of exhaust gases and the regulatory measures taken. The effort appears to be relatively too great if compared with the effort put into the prevention of traffic accidents. Does Professor Epstein agree with this?

EPSTEIN (U.S.A.)

There are two aspects to decision making. The first is the generation of unbiased and expert data by scientists. The second is the development of regulatory processes reflecting a wide range of balancing viewpoints and interests.

The question of traffic accidents relates to the second aspect. Regulatory bodies and decision making groups have the necessary information to decide whether saving of human life justifies application of available techniques such as "safety packaging" and air bags. Such decisions should properly be made in the open political arena.

DAVOUST (France)

Owing to the agricultural practices in the industrialized countries, but also to those in all countries where intensive monoculture has been introduced, plants are sick and need fertilizers and pesticides as much as a diabetic needs insulin.

Set on the chemical products road, and given the numerous scientific, political and other difficulties in decision-making which have been referred to during the symposium as regards environmental protection measures, do you think, Dr. Epstein, that the situation leads to more and more complex problems, that a choice will have to be made between health and consumption, and that the economic arguments weighed against the biological ones tip the balance in a direction not difficult to determine? Can arbitrary or authoritarian decision-making be avoided? Can decision be brought into line with the growing public conscience as regards environmental protection?

EPSTEIN (U.S.A.)

Extensive use of fertilizers and pesticides in monocultures is often economically counter productive. A part from emerging of pesticide resistance, and lack of efficacy of pesticides, contamination of food supplies and other segments of the environment often clearly result in long-term economic besides public health, damage and losses.

REEVES (U.S.A.)

I do not believe that any members of the Threshold Limits Committee of the American Conference of Governmental Industrial Hygienists are present at this Symposium. If they were, I think they would take strong exception to the statement of Dr. EPSTEIN that they are industrially influenced or dominated. In fact, no person with industrial corrections can become a voting member of A.C.G.I.H., much less of its Threshold Limits Committee.

The reason why there is a discrepancy between values on the Threshold Limits List and the Air Quality Standards is not that anyone is more callous towards the health of industrial workers than to that of the general population. TLV's are figured on a 8 h./day, 5 day/week basis, while air quality standards are figured on 24 h./day, 7 day/week basis. The general population includes infants, invalids, old people, and so forth, while industrial workers are presumably healthy and in their prime. Finally, industrial workers can be pre-screened and educated vs. the exposure hazard while the general population can not.

I agree with many of the statements and philosophies expressed by Dr. Epstein. I believe these points could be presented more effectively if he were to refrain from allegations which are inflammatory and unprovable.

EPSTEIN (U.S.A.)

The industrial bias of the A.C.G.H. is well recognized. Furthermore the TLV "standards" apply to only some 450 of the thousands of chemicals to which workers are exposed and reflect acute and sub-acute toxicity and can generally ignore long-term and chronic toxic effects. Recognition of the limitation of those standards is afforded by the recent decision of NIOSH to undertake early extensive review of the scientific basis of these "standards."

ZUNIC (Jugoslavia)

This study shows the side extent of pollution in ecological and human areas.

As we have seen, decision are of a distorted and artificial nature. Since Plato's famous socialization formula $\delta = n - 1$ and also since Montesquieu, democracy is enriched neither by theory nor by practice.

If the biological management of life is the expression of two factors in direct competition with each other, why can't the political decision be made complete by the simultaneous decision of two parties: producers and consumers.

We have an industrial monopoly, as Dr. Epstein emphasized. The fact that Man has no objective knowledge leads every civilization to its downfall. Neither society nor civilization dies in the physical sense of the work.

EPSTEIN (U.S.A.)

I thank Dr. Zunic for his perceptive comments which, in principle, I endorse.

CHANTEUR (France)

Without wishing to deny the value of the attempts to rationalize choices that evaluation studies of technical options represent, I feel that one must expose wishful thinking and stress that, in the absence of a professional opinion, they can lead to unrealistic, if not absurd decisions.

In the field of ionizing radiations, this point was given prominence by the International Commission on Radiological Protection in report no. 22 which offers an example of a realistic approach that could profitably be extended to other nuisances. Particularly in the biomedical field one should be sufficiently humble to preserve a certain empiricism. Of course, this does not exclude total independence of judgment, safeguarded by a strict division of responsibilities between the promoter organizations and those concerned with health protection.

These are the principles governing the supervision of medical radiology and nuclear energy applied daily in France by the Central Service for Protection against Ionizing Radiations (SCPRI), a technical service responsible to the Ministry of Public Health via the National Institute for Medical Health and Research.

THE USE OF QUANTITATIVE EEG FOR DETECTING LOW-LEVEL PROLONGED EXPOSURE TO PESTICIDES

JOHN A. SANTOLUCITO

Environmental Protection Agency, Research Triangle Park, NC, USA

ABSTRACT

Data were obtained from 15 minutes of anesthetized sleep EEG using three scalp electrodes positioned at mid-frontal, right and left occipito-parietal regions. Interval histograms, zero potential crossover (ZPC) rate, and right-left hemisphere correspondence were obtained using computer-assisted methods. A shift toward higher frequencies, increased ZPC rate, and an increase in the coefficient of variation of ZPC were most pronounced in carbaryl, 2,4-D, and toxaphene-treated animals. Bilateral correspondence tended to be increased by all pesticides tested.

In order to facilitate application of this methodology to occupationally exposed humans, a portable EEG was designed and constructed. The instrument is completely battery operated and will accept three channels of EEG for recording on tape cassette. The attending physician can obtain recordings before, during, and following an agricultural season, in the field, with minimal interruption of work schedules. The tape cassettes are mailed to the laboratory, played back through a physiological data acquisition unit for paper write-out and computer processing. The instrument will be described and preliminary findings will be discussed.

Introduction

Over a single ten-day period this summer, three separate meetings will have been held on the subject of pollution and the environment. There was the one in Greece which ended a few days ago, this present meeting, and a third which is due to take place next week in this very building. The programmes of all these meetings show that they conform to the current trend of being concerned with recording more accurately, detecting more quickly, and discussing yet more fully the already identified agents of pollution. No time has been set aside for defining the problems which underline pollution; the general preoccupation has been with treating symptoms rather than the disease, and, spectacular as these symptoms are, it is but palliative to treat them without seeking their aetiology. It is as if it had slipped everyone's memory that the patient is humanity itself and the wounds entirely self-inflicted.

Among the principal causes of pollution are over-population, over-exploitation of the world's finite natural resources, and an unwillingness or inability to dispose of refuse and waste products. For example, it is in the world's interest that Brazil should not reach its foolishly-declared population "goal" of 200 million by the end of the century; it is in the world's interest that its weather or radiation counts should not be affected by pollution of the upper atmosphere. The interdependence of rich and poor nations was made quite clear at the 1973 United Nations Meeting on the Environment in Stockholm. The industrialised countries talked of air and water pollution and how to decrease it; the developing countries talked of their desire to increase industrialisation; and the underdeveloped countries simply talked about how to feed themselves.

At first sight it would seem impossible to find mutually acceptable solutions when there is such disparity in development and requirements. It is evident that if the poorer countries are ever to change, then the rich nations need to change first; and people who are well off are usually unwilling to do anything which might jeopardise their own standard of living - and any change implies risk. Nevertheless, if certain aspects of the developed countries' life-style continue unchecked, it can be predicted with some certainty that they will constitute a danger to the entire world, including themselves. The industrialised nations' total dependence on chemicals exemplifies this.

Our Chemical Age

The ever-increasing use of chemicals in every sphere of activity in the industrialised countries has been accepted almost unnoticed as we move into this last quarter of the 20th century, and ours could well be called the "chemical age". The use of chemicals directly touches far more people and influences more aspects of daily life than any kind of revolution that has preceded it, and this includes the atomic age. It is profligate use of chemicals which is the root cause of pollution - whether external pollution of the environment or internal pollution of our own bodies. The industrialised nations depend on chemicals for nearly every aspect of daily living, and in addition to developing new chemicals we have growing populations and so manufacture greater quantities of these chemicals to serve them. It has become a vicious circle of more people demanding more goods, and it can be broken only if the birth-rate is controlled, if the real need for these chemicals is assessed, and if people are told that these compounds entail risks as well as benefits.

We have become accustomed to rely on chemicals for health, for homes, for transport, work, leisure, food and drink, and even for fertility and sterility. Every object of the domestic environment, including the contents of the bathroom, kitchen, and clothes cupboard, is partly or entirely synthetic; and nearly all our foods are packaged, processed, coloured, preserved, kept fresh and otherwise "improved" by the addition of chemicals. The economic - and hence political - implications of this way of life mean that if we are really concerned to decrease pollution we have to consider making radical alterations in it - alterations which would affect the work forces and distribution of labour and perhaps change the whole direction of national industries.

In such circumstances it is clearly of limited value to single out particular chemicals for special control, yet this is precisely what we are doing. Our aim should be to keep pollution at a minimum level while we re-examine the implications of continuing along our present course. Let's make our goal what we can do and not an unrealistic ideal of what we would like to see.

Internal Pollution

The advent of the chemical age has completely changed our attitudes to health and disease. We tend to think of medication in relation to the cure and treatment of disease, but in fact only one-tenth of all drugs taken in the industrialised world are for this purpose. The rest go to maintain a new concept - that of "positive health". Thanks to the pharmacological "explosion" of the post-war era, people expect to be well; to be protected from the great scourges of humanity like smallpox, tuberculosis, and malaria; to be athletic and full of energy, yet to sleep well; to be slim or muscular according to their sex; to be fertile when they wish and at all other times sterile. It is in order to attain this positive health that people swallow tons of chemicals annually. Few if any of these chemicals have ever before been taken regularly over such long periods of time by people who are healthy to start with, and the long-term effects - biological, genetic, and economic - are therefore not yet apparent or appreciated. Hence another new concept is needed - that of Internal Pollution, the abuse of the milieu interieur.

Internal pollution is brought about in three ways: by the ingestion and inhalation of the products of the already-polluted external environment; by the daily intake of chemical additives and impurities in pre-packed food; and by the vast number of medicaments taken regularly and, more often than not, unnecessarily. The last two ways could be minimised fairly easily, since it is possible to control the mechanisms involved and the economic consequences would be manageable.

The Special Commission on Internal Pollution

A number of senior scientists from different disciplines and countries, concerned at the tacit acceptance of this less visible (and hence under-publicised) kind of pollution, formed the Special Commission on Internal Pollution (SCIP) to study its consequences for a country's economy, for its national progress, and for its health - both at present and in future generations. The Commission differs from other study groups, working parties, and the like which have been appointed by governments, industries, or the international agencies in that its members represent no one but themselves. We are not beholden to anybody, we are on nobody's payroll. But if we have no partisan political axe to grind it must be stressed that neither are we politically naive; we can foresee the upheaval implied by recommending change. At the moment, however, SCIP's main concern is with its impartial investigation of the functioning and effects of the chemical age, so that more people can be better informed about it and thus more able to reach reasoned opinions and sensible decisions on its development and control.

SCIP resolved to consider the present use of chemicals under four broad headings - medication, food additives, agricultural aids, and household goods; and to relate their respective uses to the responsibility shared by the producers (that is, industry), the consumer, the government regulatory agencies, whose role is to protect the consumer, and the biomedical professions who test and prescribe many of these chemicals.

SCIP further decided to re-examine the whole concept of what we mean by "safety" in the chemical age, with special reference to the benefit: risk ratio of the different classes of compounds. With a clearer notion of what constitutes risk and what benefit, we might then see how to improve matters.

To date, SCIP has already examined medication and is at present investigating food additives and colourants. Although research is not yet complete, data is also being amassed on agricultural aids and household goods because, as will readily be appreciated, all four areas of research do to some extent overlap.

Medication

According to the pharmaceutical industry itself, if the current trend continues almost every person in the technologically-developed countries will within the next decade be on some type of daily drug regimen for the improvement or maintenance of his positive health.

We know that every drug is potentially both a healer and a killer, yet there is no disagreement about availing ourselves of potent remedies for treating serious disease: the benefits more than compensate for any attendant risks. The known toxic effect of streptomycin on the auditory nerve does not make any physician ready to withhold it in tuberculous meningitis.

Nevertheless not nearly enough attention has been given to the question of benefit and risk. Three separate factors need assessing: the benefits a compound can confer; the dangers of taking it; and the consequences of withholding it. In diseases which are invariably fatal if left untreated, these factors are relatively straightforward to weigh up. But with the improvement of medical practice such extreme situations have become the exception rather than the rule, and other aspects have to be considered.

more harmful for the organism (G.P. Babanov [2], I.P. Ulanova [14], T.V. Lomanova [7], L.N. Burkatskaya [3]).

At present, data has been obtained pointing to the practical need for a comprehensive approach to hygienic standardization of the contents of chemical compounds that are present simultaneously in several environments: fluorine (A.A. Petina [9], G.P. Pankratova [1]; benz-a-pyrene (N.Ya. Yanusheva [16], L.M. Shabad, I.V. Sanotsky [15] and others).

Besides the evaluation of the environment, an important index of the sum total action of a chemical factor for a number of substances may be the biological value of the integral MPC that has been established with the help of highly sensitive exposition tests.

References

1. G.G. AVILOVA, E.IA. GOLUBOVITCH, N.M. MALTZEVA, G.P. PANKRATOVA et al. "Atmospheric pollution by chemical compounds: adaptation and compensation" Moscow 1973, 45
2. G.P. BABANOV et al "Toxicology and hygiene of petrochemical compounds" 1972 32-45
3. IA. N. BUKRATZKAIA, V.I. MATIUSHINA, "Hygiene and toxicology of pesticides, clinical poisoning" Kiev 1968, 6th Edition, 698-703
4. A.I. KORBAKOVA, I.I. SCHUMSKAYA, G.N. ZAEVA, T.K. NIKITENKO, "Scientific basis for the current hygienic normative efforts regarding the chemical compounds present in the environment" Moscow 1971, 35-40
5. Yu. N. KORSCHUNOV, "Toxicology of the new industrial chemical compounds" Moscow 1969 2nd edition, 78-85.
6. N.G. IVANOV, A.L. GERMANOVA, V.S. POZDRIAKOV, A.M. KLYATEHKYNA et al "Adaptation and compensation of the organism confronted with chemical pollutants" Moscow 1973, 75-91
7. T.V. LOMANOVA, M.N. FROLOVA, M.A. GRITVSKI "Psychophysiology and hygiene of various work activities" 1967, 57-67
8. S.M. PAVLENKO, Hygiene and Sanitation 1972, 1. 40-4
9. A.A. PETINA, L.N. ELNITEHKIN, "Fluorine and its profilaxis" Leningrad 1967, 50-5

10. I.V. SANOTSKY, N.G. IVANOV, N.M. KARAMZYNA, V.N. FOMENKO "Scientific basis for the current hygienic normative efforts regarding the chemical compounds present in the environment" Moscow 1971, 63-68

11. E.I. SPYNU "Hygiene, application and toxicology of pesticides; clinical poisoning" Kiev, 1968, 103-9

12. O.A. KRYLOV, The Setzenova Journal 1966, vol. 52, No. 7, 906-910

13. L.A. TIUKOV, V.V. KUSTOV. "Methods for the determination of the toxicity and danger of chemical compounds" Moscow 1970, 231-45

14. I.P. ULANOVA et al, "Adaptation and compensation of the organism confronted with chemical pollutants" Moscow 1973, 64-75

15. M.I. SCHABAN, I.V. SANOTSKI et al. Hygiene and Sanitation, 1973, 4, 78-81

16. N. Ya. YANSCHEVA, Hygiene and Sanitation, 1972, 7, 87

BEHAVIORAL METHODS FOR INVESTIGATING ENVIRONMENTAL HEALTH EFFECTS

BERNARD WEISS

Department of Radiation Biology and Biophysics, University of
Rochester School of Medicine and Dentistry, Rochester, New York
USA

ABSTRACT

One may conceive of three phases in the assessment of behavioral changes induced by environmental contaminants. The first is the non-specific, or screening phase, during which a search is made for general CNS effects. The methodology employed stresses relatively simple techniques, partly because, for some agents, any CNS activity prohibits their use and partly because one aim is to estimate the relevant range of dose levels. These techniques encompass observational tests of unlearned behavior, and relatively simple learned behavior.

The second phase focuses on the specific functions that are affected; for example, sensory and motor function and complex discriminative processes. The pertinent techniques almost all involve highly-trained animals, and advanced instrumentation, including computers.

The third phase focuses on human health. Its purview extends from laboratory studies of complex functions to what might be called behavioral epidemiology. Naturally, it is the most difficult phase.

1. Introduction

Numerous environmental insults and contaminants express their actions through alterations in behavior. These effects range from subtle, nonspecific symptoms to overt, easily discernible behavioral disruption. The site of action can either involve the central nervous system (CNS) directly, as with organic mercury poisoning, or indirectly, as with respiratory irritants that induce performance impairment by provoking discomfort.

Only recently has it been recognized in the United States and most of Western Europe that behavioral measures could play a significant role in the assessment of toxic processes. Part of this new visibility arises from the pressures on public agencies to set standards on the basis of minimal interference with health, not simply on the basis of clear mortality and morbidity. Part is due to the recognition that new techniques are now available, largely from psychopharmacology, with which to study chemical influences on behavior. A significant contribution also comes from an awareness that standard setting in countries such as the U.S.S.R. historically has been guided by evaluations of CNS function.

I plan, in this paper, to survey some of the ways in which behavioral assessments may contribute to the resolution of certain issues posed to toxicology in the context of environmental health. The framework I will employ is the sequence of questions to be answered with the introduction of a new chemical agent presumed to involve human exposures. Other effects on the total ecosphere are set aside for the present.

I conceive of such an assessment as encompassing three phases. The first is the screening phase, which corresponds to the preliminary observations undertaken in the pharmaceutical industry when a new compound is being scrutinized. The second is the specific function phase, during which, if required, detailed assessments are made of systems that seem to be targets of undesirable actions. Such assessments encompass complex behavioral processes in animals and the examination of sensory and motor deficits. The third phase deals with human susceptibility and its parameters, both in the field and in the laboratory.

2. Screening Phase

Although a relatively straightforward, somewhat standardized approach to CNS drug screening has been evolved by the drug industry, it falls short for environmental agents. Weighing risks and benefits is a much different matter for a therapeutic chemical, used under limited condi-

One of the patients, when she first appeared in the laboratory, gave us records such as the one shown in the upper section of Figure 9. This patient was unable to keep the applied force between the designated limits of 10 and 40 grams. Nine months later, with no intervening exposures, performance greatly improved (lower section of Figure 9).

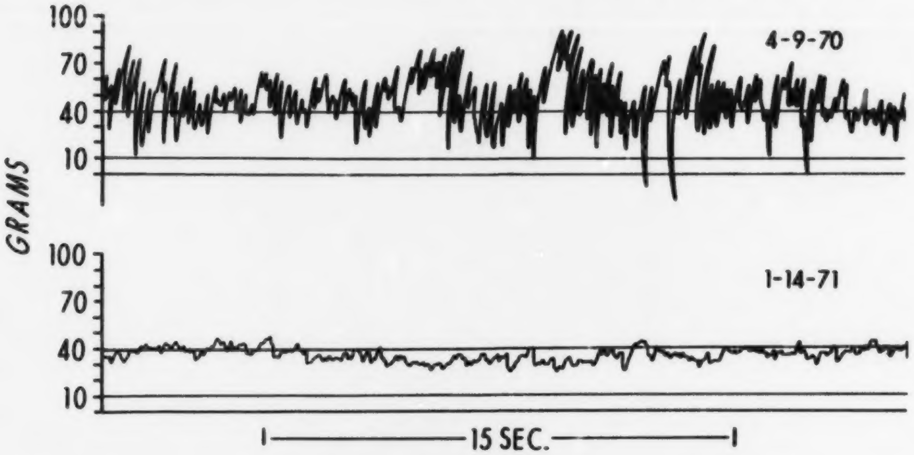


Figure 9. Polygraph tracings of a patient (see Figure 8 apparatus) exposed to mercury vapor (upper) and 9 months after cessation of exposure (lower).

A more useful way of tracking progress is shown in Figure 10. The patient whose record is shown in Figure 9 appears here as "Mrs. T." "Mr. T." is her husband, who served as a control. "Mrs. N." is a co-worker. The figure shows that the proportion of time within the prescribed limits attained stable values in about two months, during which the plasma level of mercury fell to about half its earlier value. "Mrs. N." showed a more rapid response, but her plasma levels were lower, and, in addition, she was treated with the chelation agent, n-acetylpenicillamine.

A further parameter of quantification appears in Figure 11. These charts represent a frequency analysis of the tremor. The earlier evaluation shows multiple peaks and a huge variance. The later one shows a much narrower distribution of power.

This demonstration testifies to the utility of quantification and precise measures of motor function. Similar examples for discriminative functions can be extracted from the literature on carbon monoxide [14].

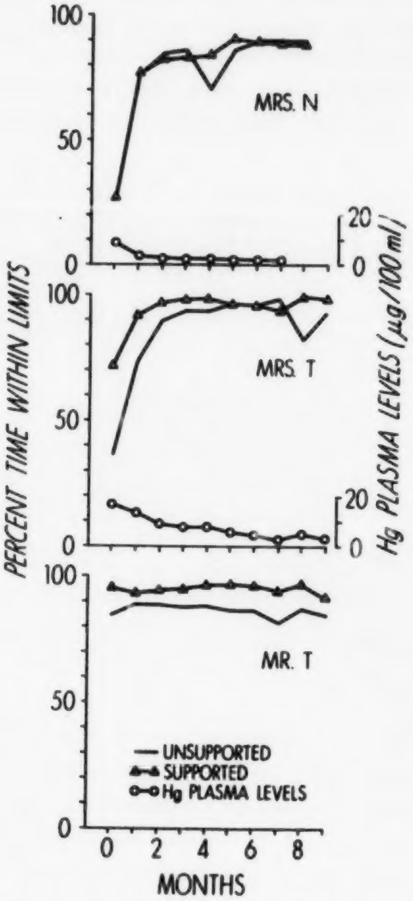


Figure 10. Performance of two exposed women and an unexposed man expressed as proportion of time spent within designated force limits on the apparatus shown in Figure 8. Note the relation between improved performance and the decline in plasma mercury.

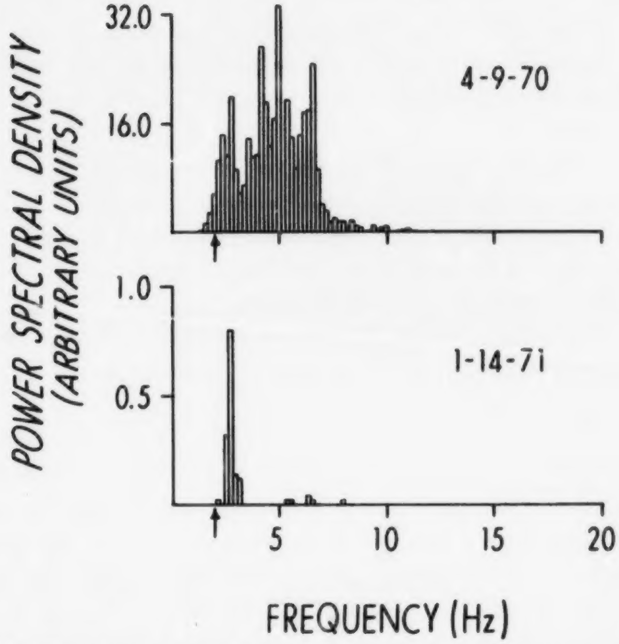


Figure 11. Power spectral analysis of the tremor shown in Figure 9. This chart shows the distribution of power (variance) over frequency. The effects of mercury vapor exposure were not simply to increase tremor amplitude.

Laboratory studies such as those adduced above are, I will admit, projects of minimal vexation compared to the frustration presented by studies in the field. When exposed individuals cannot be brought into the laboratory for testing, or when the symptoms do not lend themselves to laboratory studies, we have to turn to other techniques. This is especially true when dealing with the relatively nonspecific complaints associated with many early intoxications.

Mercury vapor exposure, for example, engenders a collection of symptoms so well known in the clinical literature that it even has a label--erethism. Yet, the components of erethism sound just like a catalog of so-called neurotic complaints: fatigue, irritability, anxieties about social relationships, numerous mild somatic complaints, and, in general, a marked lability in behavior. Carbon disulfide and lead are other examples of substances that may produce such complaints.

Although I would hardly minimize the obstacles to reliable measurement of this class of variables, the methodology is a standard procedure in psychology. Many test and survey instruments are developed each year according to these procedures. Unfortunately those aimed at some of the questions that environmental health specialists view as important are not pertinent because they tend to focus on enduring traits, not the assessment of change.

There are, however, enough materials available to provide a firm beginning to the design of a useful questionnaire instrument. Examples such as Goldberg's General Health questionnaire [15] and the Symptom Distress Check List [16] can be used as guides to useful items. Once refined, moreover, such an instrument could be validated in more easily quantifiable ways than psychological tests typically have access to: body burden measurements, days of absenteeism, exposure duration, and so on.

5. Conclusions

I have surveyed the range of what I believe behavioral toxicology encompasses in the broad context of environmental health. Naturally, I have had to ignore many fascinating and useful aspects, and creative workers, in order to keep this paper within bounds. I hope, however, that I have helped familiarize some of you from other specialties with the ways in which certain vital issues in environmental health are joined to behavior science.

Acknowledgment

The preparation of this paper was supported, in part, by Grant MH-11752 from the National Institute of Mental Health, Grant NS-08048 from the National Institute of Neurological Diseases and Stroke, Grant GI-30097X from the RANN Program of the National Science Foundation, and in part by a contract with the U. S. Atomic Energy Commission at the University of Rochester Atomic Energy Project and has been assigned Report No. UR-3490-541.

7. Les techniques actuelles de mesure dans l'environnement (monitoring) sont parfois encombrantes: elles doivent être mieux adaptées à l'évaluation numérique des expositions et par ailleurs des nouveaux indicateurs de pollutions, si possible polyvalents, doivent être recherchés dans le milieu et chez l'homme pour faciliter les enquêtes épidémiologiques et les rendre plus efficaces;

8. parmi les effets à long terme, le phénomène de vieillissement accéléré sur le plan physique et mental n'a pas été suffisamment pris en considération comme peut être aussi, certaines répercussions imprévues sur l'ontogenèse; une approche fondamentale est souhaitable en même temps que des enquêtes épidemiologiques orientées;

9. tout en reconnaissant qu'il vaut mieux prévenir que guérir, et qu'il vaut mieux éviter la pollution que la combattre, il n'empêche qu'il peut être précieux de chercher sur le plan biologique et physiologique des parades et des remèdes à certaines contaminations d'autant plus que certaines, d'origine naturelle, sont inévitables.

En terminant cet exposé, je voudrais insister au nom de mes collègues et au nom des êtres que nous voulons protéger sur l'importance de *l'information centripète* d'une part, et sur la constitution d'une banque de données d'autre part. Trop de données disponibles au niveau de l'industrie et de l'agriculture ou au niveau de la médecine professionnelle ou préventive, pour des raisons diverses ne sont pas communiquées aux responsables des études épidémiologiques. Par ailleurs, le médecin praticien, peut être, parce qu'il n'est pas suffisamment préparé, néglige de transmettre des informations qui seraient souvent précieuses; son attention devrait être particulièrement portée sur l'observation des groupes à haut risque et sur l'intérêt du "monitoring" biologique. Souhaitons que cet appel suffise et qu'une réponse bienveillante permette d'éviter d'aboutir à des mesures réglementaires pour obtenir ces diverses informations.

Corrélativement, la constitution d'une *banque de données toxicologiques* par collecte aléatoire des coïncidences suspectes nous paraît indispensable, allant de pair avec la surveillance régulière d'échantillons de population représentatifs ou correspondant à des groupes particulièrement sensibles. Une telle banque de données serait précieuse pour aider l'O.M.S. dans ses efforts et constituerait un fondement précieux pour les enquêtes épidémiologiques que nous suggérons.

Souhaitons que les efforts entr [illegible] e part et d'autre de l'Atlantique se conjugent et [illegible] nt dans ce sens et que cette réalisation soit une des [illegible] ations de ce symposium qui n'a pu aboutir que par un [illegible] ation intense des trois organismes intéressés à ce s [illegible] t grâce au dynamisme sympathique des organisateur

CONCLUSIONS AND REFLECTIONS OF THE SCIENTIFIC ADVISERS

Presented by

Prof. A. LAFONTAINE
Belgium

(translation)

In relation to the protection of man and the environment, criteria may be defined as judgements based on scientific data, reflecting a relationship (expressed as far as possible numerically) between the exposure of a target to an agressive factor and the resulting risk and/or unfavourable or undesirable effect on this target; the establishment of criteria is the first of the steps which, in cartesian logic, should result initially in the setting of quality objectives, followed by the establishment of standards, rules and codes of good practice.

Since man's health, individually and collectively, is unquestionably the most important issue at stake, it was logical that the three organizations responsible for the symposium should be concerned above all to collect existing scientific knowledge in order to make progress in establishing relationships between exposure to pollutants and direct and indirect effects on health, to achieve the most rational possible assessment of the risks, and, at a later stage, to decide on action programmes to prevent or reduce pollution or limit its effects.

Experience having unfortunately demonstrated the often fragmentary nature of information at hand and the scant use that could be made from many experimental studies and certain epidemiological studies, the sponsors were fully aware of the difficulties which would arise, all the more so as there is a risk of certain less relevant factors becoming mixed up with the strictly scientific aspects. They also knew that a great deal of research had been carried out for other reasons than the desire to establish criteria. Therefore, in addition to the new data which might be collected, it was their intention:

a) to provide for better planning more specific motivation, and more efficient and strictly objective orientation of research work;

b) to discover the nature and size of the gaps in present knowledge;

c) to identify as far as possible the fields in which it is necessary to act, in view of the urgency or priority nature of the problems, and those for which existing data, even if they are still incomplete, suffice for action to be taken.

Despite all the difficulties, despite the uneven and at times disparate nature of the papers presented, the scientific advisers nevertheless consider the result as highly positive, in view of the diversity of the objectives envisaged.

New data have come to light concerning, inter alia, urban atmospheric pollution, the dangers of heavy metals, acousitc nuisances, experimental techniques, indicators of exposure, biological measurements and new experimental approaches to behavioural phenomena. New problems have been tackled, such as those caused by biphenyl polychlorides or vinyl chloride. Even greater contributions were made, however, in the matter of the scientific data required for decision-making in health protection and the identification of fundamental gaps in our knowledge, the future direction of research work and the fields to be explored in order to lay the necessary scientific foundation for reflection and decision-making.

We would, however, be lacking in objectivity if, before embarking on various reflections and suggestions, we did not draw attention to certain weaknesses in the documents submitted, such as the one-sided obsession with certain subjects like heavy metals or certain sectors such as atmospheric pollutants. These could probably result from scientific enthusiasm, political emphasis or public pressure. On the other hand, little attention was paid to other subjects such as nitro derivatives, nitrosamines, mycotoxins or manganese. Despite their topical interest, certain sectors like solid residues and soil contamination did not preoccupy the authors, and today the toxicology of water intended for human consumption might to the unaware seem like a problem of the past. Other sectors such as medicinal products, food additives and certain harmful effects such as those of ionizing and non-ionizing radiation were not considered during this symposium, chiefly on account of a now traditional compartmentalization, which ought to be sacrificed to a more global approach to the problems, since the target of these various nuisances is the same, namely, man and the human race.

However, although the scientific advisers regret the sometimes excessive tendency of environmental problems to be spread out over a considerable number of organizations, they would also like to draw attention to the cooperation which has come into being between the three organizations responsible for the symposium and to thank them for the exceptional opportunity given to research workers from Europe, America and, thanks to the WHO, the whole world, to meet and seek to establish health criteria - criteria uninfluenced by any socio-economical or political consideration - common to all men in this "one world" of ours, and work together in the most fraternal and cooperative spirit.

Among the many reflections inspired by the discussion held during the symposium, we believe that apart from the implementation of action programmes concerning the list submitted by the WHO of substances for which information must be collected and research conducted, the following particular points deserve to be stressed:

1. It is of the utmost importance to express oneself clearly and the need for a glossary defining terms used in environmental studies was felt yet once again.

2. It too often happens that each pollutant and each sector are considered independently and it is forgotten that man acts as an integrator of nuisances: the same toxic agent may reach him in different ways and various degenerative agents, including those linked to certain habits (use of tobacco for example), may affect the same target organ. The risks linked with chemical and physical pollutants must not make us overlook biological and microbiological risks. The idea of body burden, of total incorporation, must become general, as must the idea of allowable doses per day, week, month or year, depending on the case,

Furthermore, to the concept of concentrations in the atmosphere, in water or in the soil, one must add that of the toxicological capacity of a medium, a region or a basin(especially for non-degradable substances), that is the total amount of polluting substances which this medium, region or basin can tolerate without irreparable damage.

3. The discussions stressed the need for methodological developments, especially with regard to epidemiology, the use of animals models pre-testing and the balance -sheet of adventages and disadvantages:

a) epidemiological techniques are of fundamental importance, not only to assess the direct or indirect influence of pollution on health, but also to identify new dangers or harmful influences and to appreciate the effectiveness of the actions undertaken. Epidemiologists should be able to rely more extensively on information supplied by an informed public and by a body of informed practising doctors: general clinical practice and workplace observations can be of cardinal importance, but do require some preparation of the medical profession. The implementation of multinational epidemiological programmes may be very helpful in assessing the concomitant effect of other factors, such as ambient conditions or geographical and climatic influences, etc.

b) development of the use of animals for simulating human diseases in toxicological tests is indispensable for a better understanding of the effects observed and to ensure maximum effectiveness when pre-testing new products and new technologies. These tests must be devised in such a way as to remain closely related to the epidemiological studies;

It is possible that this kind of information may require future standards for combinations of pollutants. It would require methods to measure the constituents of the important combinations of pollutants simultaneously. It would require field networks to simultaneously monitor the constituents of important combinations, source inventories of all constituents of the combinations, models linking sources of all constituents of the combinations to ambient levels, joint control plan strategies for all constituents of the combinations, and adequate enforcement plans.

We may find that scientific information to support regulatory strategies for control of combinations of pollutants will be many times more difficult to obtain than information for single pollutants. Indeed, we may be well advised to begin now to plan systematically for the collection and analysis of such data.

If the harmful combinations of pollutants are known to exist in certain regions, perhaps we can use the level of a single pollutant of the combination as an index of the level of the combination. However, the accuracy of this approach will have to be experimentally evaluated.

We have seen this week that epidemiological studies reflect progressively greater degrees of sophistication concerning their design and methodologies both for assessing the pollutant exposures and identifying and quantifying health effects. We believe that the state-of-the-art has now been sufficiently developed to the point where studies involving common pollutants can and should use standardized methodologies concerning both the physical/chemical monitoring and the biological effects assessment. Such an approach will allow the development of standardized data bases utilizing the multiplicity of studies conducted throughout the world. It will, therefore, expedite our attainment of knowledge and allow for the more efficient use of our seperate limited research resources. Some effort of this nature is already underway. For example, the cooperative epidemiology studies presented at this meeting being conducted by the CEC and the WHO. In the area of environmental monitoring, the WHO air pollution monitoring program is using regional and many other intenational air monitoring sites where there has been cooperative agreement on standardized sampling, analytical, and data management systems. EPA, serving as the WHO International Reference Center for Air Pollution Control, is intimately involved in this program as well as with the WHO Air Quality Criteria Program. I am sure other examples could also be cited. Such cooperative efforts involving standardized protocols should be expanded on both the national and international level.

At the present time, most effort toward standardization have concerned monitoring programs, health questionnaires, and to a more limited degree, pulmonary function measurements. These should be continued and improved. For example, similar efforts should be applied to many other biological parameters being used as health indicators, as well as to biological sampling and analysis and the statistical treatment and presentation of the basic data. The degree of success achievable by any of these efforts will depend totally upon the inclusion of an adequate quality control program. Standardized methodology with quality control can benefit all of our criteria and standard development activities.

Of course, this recommendation is only intended for applied research and not meant to disregard the obvious need for continuing efforts in the development of new or the improvement of existing research methodologies. Results from this area of more basic research should, after being proved effective in the field, be incorporated into cooperatively developed standardized protocols.

The magnitude and difficulty of research needed to provide the necessary information base for pollution control tells us that we cannot afford the time or resources given to investigations, that do not contribute directly to the needed information base. As our research becomes more difficult and our regulations, and the society to which they apply, become more complex, it is necessary for the scientific community to assess its status and systematically determine its future direction. To do otherwise, that is to say, pursue our investigations separately according to separate interests and techniques and without coordination is not only wasteful of time and resources, but promises to yield results that lack practical usefulness because of basic differences in objectives and methods.

A systems analysis approach to the identification and solution of future problems could assure application of research effort to the most critical needs. It would also assure the integration of the necessary interdisciplinary contributions to each study. It would tend to eliminate project activity of doubtful significance and the collection of questionable data.

One practical way to internationally unify the direction of research is to internationalize the preparation of criteria documents which would include the assessment of current information and identification of gaps in knowledge which would serve as needs to be fulfilled through research. A practical way to this achievement would be for all member countries to participate in the WHO Air Quality Criteria Program.

I would like to make a comment on the future of meetings such as this. This symposium provided a complete overview of the advances to date of research on the health effects of environmental pollutants. It was necessarily large and comprehensive. It has served its purpose well. We now know where the state-of-knowledge of this subject stands, and it has suggested to us concepts by which we can guide future efforts. It would seem that because this symposium has so well accomplished its purpose, consideration of future meetings in this subject area might be in terms of specific pollutants, or classes or combinations of pollutants, and their effects, or in terms of areas of pollutant control, for example, pollutants associated with particular industries or sources.

Again, I wish to express deep thanks to all the organizers and the participants in this highly succussful symposium. It is only through such extensive and enthusiastic cooperative participation that we can have full confidence in the results and ideas that have come forth from this monumental effort.

REMARQUES FINALES

DR. P. RECHT
Directeur de la Protection Sanitaire,
Commission des Communautés européennes
Luxembourg (Grand-Duché)

A l'issue d'un Symposium, harassant pour les organisateurs et les participants en raison de la densité du sujet, du rythme des sessions, du nombre des communications et de l'intensité des discussions, il est certain que nous avons tous un grand nombre de réflexions à présenter. Ceux qui m'ont précédé ont exprimé de façon excellente les réactions et les commentaires que méritait une telle réunion.

Parlant le dernier, il m'est facile de m'associer au nom de la Commission des Communautés européennes aux déclarations qui viennent d'être faites par mes deux collègues et amis de l'Organisation Mondiale de la Santé et de l'Agence de la Protection de l'Environnement des Etats-Unis. Je souscris entièrement à ce qu'ils ont dit et je me permets d'ajouter que nous pouvons nous féliciter d'avoir trouvé dans la mise sur pied de cette conférence la clef d'une collaboration tripartite efficace et bénéfique pour l'avenir.

Ce Symposium présentait des risques qui sont apparus au moment où le Comité organisateur et les conseillers scientifiques ont examiné un nombre impressionnant de rapports et de communications et ont dû faire un choix dans les propositions qui ont été envoyées.

Il est indéniable qu'il y a dans les communications que vous avez entendues pendant cinq jours une dispersion qui indique que les problèmes de l'environnement ont des aspects multiples et complexes et que dès lors il était indispensable de tenter la recherche d'une méthodologie commune pour les affronter.

Malgré le caractère positif des résultats qui ont été apportés, nous sommes forcés de reconnaître que sur un très grand nombre de sujets, il n'y a pas encore de réponse satisfaisante du point du vue scientifique. Cette remarque ne doit pas être considérée comme un reproche à l'encontre de la recherche scientifique dans le domaine de l'environnement. C'est une constatation qui doit nous conduire, cher Monsieur Dietrich, à demander à l'O.M.S. d'intensifier encore son action et de jouer un rôle indispensable dans l'établissement de critères et de normes sanitaires communes. Il est temps que dans le domaine de l'environnement, les problèmes de la protection de l'homme et de son milieu prennent leur place véritable et soient traités par ceux qui en ont la compétence et la responsabilité.

Preceding page blank

exposure to undetected or untested pollutants in the environment. Such surveys are complicated by the long interval which may elapse between exposure and subsequent adverse effects. This may be measured in decades for cancer and in generations for mutations.

Epidmiologic techniques serve to detect trends or fluctuations in mortality, morbidity or disease patterns. Provided that clear differentials in exposure levels to pollutants exist in the general population, epidemiology may then correlate particular toxic effects with particular pollutants; the association between heavy cigarette smoking and lung cancer is a classic example of such a relationship. However, these relationships are more difficult to establish when exposure differentials are minimal, as with a food additive consumed at more or less similar levels by the general population. Additionally, logistic considerations, quite apart from inadequate current surveillance systems, may limit the utility of epidemiological approaches even when temporal or spatial clusters of adverse effects have developed. Disquietingly, no major known human teratogen-- X-rays, German measles, mercury or thalidomide-- has been epidemiologically identified, even in industrialized countries with good medical facilities.

5. Contrast Between Environmental and Occupational Health Standards

A fundamental dichotomy, both scientific and moral, exists between current approaches to standard-setting for the working population and for the population-at-large (Epstein [8]). In spite of their major inadequacies, standards that have been developed for the protection of the population-at-large against adverse effects from exposure to a wide range of chemical pollutants and products are generally predicated on the availability of an adequate data base. Necessary information includes chemical composition of such products, labelling and disclosure of ingredient identity, and on the testing of such products in animals for acute and chronic toxic effects prior to their release into commerce. For agents producing acute and chronic toxicity per se in animals threshold or no-effect levels are determined and standards are then developed, generally, based on 100 - fold safety margins. Agents which induce carcinogenic effects in appropriate animal tests or which are known to be carcinogenic to man are generally banned from commerce, as no level of exposure can be considered safe.

These general requirements are in striking contrast to the situation for occupational health standards. Standards exist for only a small fraction, about 450, of chemicals to which workers are exposed. Illustratively, a "Toxic Substances" publication of the National Institute of Occupational Safety and Hygiene (NIOSH) listed approximately 8,000 known chemicals used in industry in 1971 and approximately 25,000 in 1973; these figures clearly underestimate the numbers of chemicals to which occupational exposure can occur. Most Federal U.S. standards are based on approximately 450 threshold limit value (TLV) standards developed by the industrially-oriented, if not dominated, American Conference of Government Industrial Hygienists (ACGIH); these TLV standards are often referred to as "proprietary", reflecting their narrowly focused "trade" origin.

The concept of adequate safety margins is scarcely, if at all, reflected in occupational, in contrast with general environmental standards. This is well exemplified by reference to current occupational standards on lead, 150 $\mu g/m^3$, in contrast with proposed general environmental standards in California, which are 100-fold lower (Epstein [8]). Furthermore, once occupational standards have been developed and promulgated there is currently no effective method for implementing them. The tacit reliance on voluntary compliance is in part, perforce, an expression of imposed fiscal, personnel, and grade ceilings in the Occupational Health and Safety Administration (OSHA), and in part an expression of the philosophy of the dual standard.

Finally, there are no current requirements for "pre-testing" or screening chemicals prior to their manufacture and use by industry, nor are there even general requirements for open disclosure of the identity of chemical agents to which workers are exposed. This is clearly contrary to the intent of the Occupational Safety and Health Act, effective April 28, 1971, which mandated the provision of a safe and healthy working environment. No such assurances can possibly be made in the absence of information as to the chemical nature and possible biological effects of these exposures. In the absence of "pre-testing", the worker is unwittingly used as an involuntary test subject, to whom test data are not made available, if indeed they are ever collected and analyzed. Recognition of adverse effects in retrospective epidemiological studies, is *post hoc*. These human experiments are unnecessary and

The electroencephalogram (EEG) is easily obtained, non-destructive, and non-invasive. Consequently, it is particularly suitable as a biological monitor. The available literature is supportive of the conclusion that the electrical activity is one of the most sensitive indicators of an altered functional state of the brain in the intact animal. The EEG has been altered in repeated chronic exposure experiments with DDT [1], endrin [2], and dieldrin [3] in which clinical signs of toxicity eventually appear. Specific anomalies in the EEG related to occupational exposure to dieldrin, aldrin, and endrin without clinical signs of intoxication have also been reported [4]. Workers occupationally exposed to organophosphate compounds repeatedly, showed EEG changes similar to those seen after acute exposure [5]. Non-human primates fed selected pesticides for 18 months exhibited alterations in EEG frequency distribution and right-left hemisphere waveform coincidence [6].

As a result of the pioneer efforts of Walter [7] and Drohocki [8], analyzer systems are readily available today. Such systems are used frequently in animal experiments for the quantification of EEG. However for human use, a remaining problem is its easy acquisition from large numbers of the general population in a form accepted by automated data processing systems.

The objective of this research is first to establish quantitative EEG indicators of prolonged, low-level exposure to pesticides using non-human primates and second, to apply the methodology developed to pesticide exposed humans.

Squirrel monkeys (Saimiri sciureus) were placed on low level daily intake of selected pesticides in 1968. A contemporary control group has also been maintained for evaluation of treatment effects. Comparison of EEG's between treated and control groups was chosen instead of comparisons of treated monkeys with their own pre-treatment control period to avoid confusion with age-associated changes.

The dosing regimen is summarized in Table I.

Bipolar EEG recordings are made with three subcutaneous, platinum needle electrodes placed in mid-frontal (MF), right, and left occipito-parietal (RO-P and LO-P) locations. Thus, three channels of EEG, representing RO-P x MF, LO-P x MF, and RO-P x LO-P, are obtained. This arrangement optimizes the recovery of all EEG waveforms with the fewest number of electrodes. It has been shown that placement of electrodes at

TABLE I. Protocol for Squirrel Monkeys Receiving Chronic, Low-Level Intake of Selected Pesticides.

Pesticide	Daily Dose* (mg/kg Body Weight)
Parathion (6)**	0.03
Carbaryl (6)	0.007
Dieldrin (5)	0.1
Toxaphene (6)	1.0
2,4-D (6)	0.2
Lindane (5)	0.05
Control (7)	--

*Pesticide administered per os, 6 days/week

**Number of animals

the front and back of the head form a lead pair almost equally sensitive to sources anywhere in the entire brain [9], and right and left derivations permit assessment of hemispherical bilateral symmetry.

At the time of recording, monkeys are given 1.0 mg/kg Sernylan[1], i.m., to immobilize them. They are then anesthetized with Surital[2], i.v., to loss of blink reflex and predominantly abdominal breathing. Scalp electrodes are affixed and 15 minutes of EEG are taken using a Beckman, Type-R Dynograph. The anesthetized EEG is stable with time for a given depth of anesthesia as has been found by others [10]. The data presented here were obtained from on-line computer assisted interval analysis of five minutes of the recording after three years of pesticide exposure.

It can be seen in Table II that the EEG from 2,4-D, toxaphene, and carbaryl-treated animals shifted toward higher frequencies. This was generally accompanied by a decreased amplitude of the high voltage, slow waves seen in anesthetized sleep. Dieldrin was unique among the pesticides tested in showing synchronization of the EEG, i.e., increased amplitude of the high voltage, slow waves < 1.5 Hz. No other consistent amplitude differences were seen between treatment groups.

One is the question of the relative dangers and benefits of alternative therapies; another is the severity of the disease which may vary from inexorably lethal, like cancer of the stomach, to fatal at a later and uncertain stage, like Hodgkin's disease and some leukaemias; from the incapacitating like the arthritides to the merely inconvenient, like some skin conditions. Other factors include how long the disease may be expected to last if untreated; is it acute and completely curable with the appropriate therapy? Is it short term chronic and curable? Or long term chronic and controllable rather than curable? How much risk is acceptable in therapy which will sufficiently control the disease to give the patient a reasonable quality of life? Which will end his life first - the disease or the drug? Is it possible that social opinion may change during the natural history of a patient's chronic disease?

Side Effects

These questions are still further complicated by the fact that no two human beings are physiologically identical and hence will not react identically to the same drug. In a sense, each new administering of medication is an experiment. So in view of the pharmaceutical companies' startling prediction just quoted there is good reason for considerable concern over the upsurge in iatrogenic conditions. A conservative estimate has it that some 5-10 per cent of all patients admitted to hospital in the UK and the United States are there because of the side-effects of drugs they are taking: and of these patients between 2 and 3 per cent die. Some of the drugs have been prescribed by the patients' own doctors, while others have been bought over the counter. Up to 5 per cent of a typical British general practitioner's patients may consult him with iatrogenic disease, and of patients already in hospital as many as 18 per cent suffer adverse reactions to drugs, according to surveys in the US and Canada. A British survey found similar reactions in 10.2 per cent of a sample of 1,160 patients. Two to 3 per cent of congenital malformations are attributable to drugs and chemical pollutants.

The Pharmaceutical Industry

What are the reasons for this level of apparent failure in a field supposedly as minutely researched as pharmacology? It is fashionable, especially in journalistic circles, to pin the blame on the pharmaceutical industry itself, if only because evidence of price-fixing and substantial profits induce people to look no further for a scapegoat. This attitude is not justified. We have found that the ethical pharmaceutical industry maintains high overall standards of manufacture and testing. Furthermore, our investigations found no support for the impression common since the Thalidomide tragedy that the tests carried out on new drugs are ineffective or inefficient. In fact, we can state categorically that the tests are as good as our present state of knowledge allows.

We found the problem to lie not with the tests, but with the testers. Many testers succumb to the human weaknesses of inefficiency and lack of conscientiousness - especially if their salaries are poor and their career-structure unestablished. They are no different from the society which produces them. In addition, we have found that many pre-clinical tests are not carried out by the scientist in charge of the project; he reads the results brought to him by his technicians. We have noticed this to be particularly true of industry, where there is rigid adherence to a hierarchical system.

The truth is that many research scientists are, by nature of their intense specialisation, unqualified to correlate diverse results, to cross-transfer, or to recognise anomalies thrown up by different testing techniques. The picture is one of so many tests that no single scientist is competent to make a final assessment of the drug under examination. The pharmaceutical industry itself complains of toxicity tests so numerous that the very volume of work gives the regulating agencies an assurance of quality that could be illusory. In fact our experience has shown that the perspicacity to pick the right animal and conduct the correct study in depth in a small group of animals is far more likely to provide the desired information than is sheer numerical weight of different tests. This fact is well recognised, yet it is still not accepted practice.

Clinical Pharmacology

However, the testers are not the only ones at fault. In fact, there are twin culprits - the testers and also the doctors. On the medical profession's side, all is far from well. In May 1973 it was reported that some 30 per cent of American doctors doing clinical trials of new drugs whose work was spot-checked by the FDA were guilty of a range of unethical practices, including giving wrong dosages and falsifying records. In fact, of all the reports submitted, in one-third the trial was never done at all, in another third it did not follow the manufacturer's protocol, and only in one-third were the results of any value. In some cases the doctors have been so slick that they were able to "take care" of patients in America while attending meetings on extended European vacations.

tions, than for an agent that might be dispersed widely, linger for many years, and expose large segments of the population. Such considerations direct one to a sequential evaluation such as that diagrammed in Figure 1. This is a flow diagram devised for a forthcoming publication from the U.S. National Academy of Sciences, The Evaluation of Chemicals for Societal Use, prepared for the Environmental Protection Agency [1].

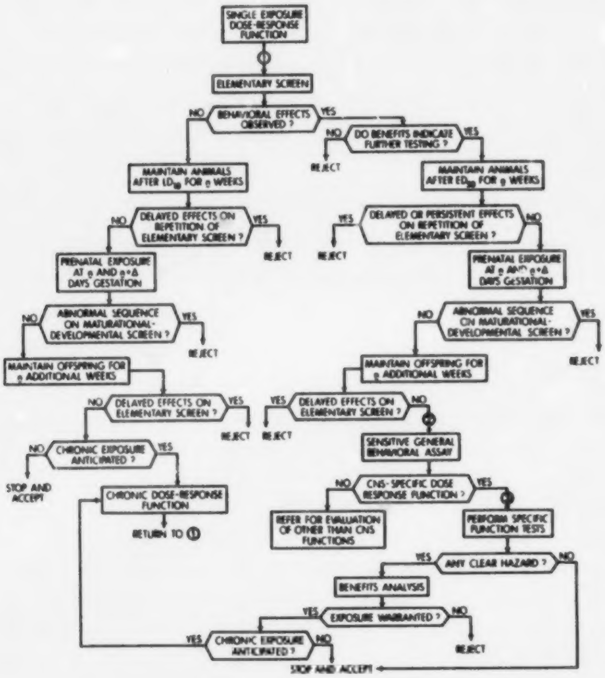

SINGLE EXPOSURE DOSE-RESPONSE FUNCTION
①
ELEMENTARY SCREEN
NO
BEHAVIORAL EFFECTS OBSERVED ?
YES
NO
DO BENEFITS INDICATE FURTHER TESTING ?
YES
REJECT
MAINTAIN ANIMALS AFTER LD$_{10}$ FOR n WEEKS
MAINTAIN ANIMALS AFTER ED$_{50}$ FOR n WEEKS
NO
DELAYED EFFECTS ON REPETITION OF ELEMENTARY SCREEN ?
YES
REJECT
YES
DELAYED OR PERSISTENT EFFECTS ON REPETITION OF ELEMENTARY SCREEN ?
NO
REJECT
PRENATAL EXPOSURE AT n AND $n+\Delta$ DAYS GESTATION
PRENATAL EXPOSURE AT n AND $n+\Delta$ DAYS GESTATION
NO
ABNORMAL SEQUENCE ON MATURATIONAL-DEVELOPMENTAL SCREEN ?
YES
REJECT
NO
ABNORMAL SEQUENCE ON MATURATIONAL-DEVELOPMENTAL SCREEN ?
YES
REJECT
MAINTAIN OFFSPRING FOR n ADDITIONAL WEEKS
MAINTAIN OFFSPRING FOR n ADDITIONAL WEEKS
NO
DELAYED EFFECTS ON ELEMENTARY SCREEN ?
YES
REJECT
YES
DELAYED EFFECTS ON ELEMENTARY SCREEN ?
NO
REJECT
②
NO
CHRONIC EXPOSURE ANTICIPATED ?
YES
STOP AND ACCEPT
CHRONIC DOSE-RESPONSE FUNCTION
RETURN TO ①
SENSITIVE GENERAL BEHAVIORAL ASSAY
NO
CNS-SPECIFIC DOSE RESPONSE FUNCTION ?
YES
③
REFER FOR EVALUATION OF OTHER THAN CNS FUNCTIONS
PERFORM SPECIFIC FUNCTION TESTS
YES
ANY CLEAR HAZARD ?
NO
BENEFITS ANALYSIS
YES
EXPOSURE WARRANTED ?
NO
REJECT
YES
CHRONIC EXPOSURE ANTICIPATED ?
NO
STOP AND ACCEPT

Figure 1. Flow diagram illustrating a proposed sequential testing protocol for behavioral effects.

As in conventional screening, we recommend inclusion of CNS observations in the total acute toxicity studies. Such observations would include simple indices of locomotor impairment, neurological indices such as tremor, ptosis, and convulsions, alterations in various reflexes, and disorders of regulation.

Instead of stopping with these observations, however, an environmental agent should be further examined for delayed effects. We are all familiar with agents capable of producing damage, not immediately after exposure, but following a prolonged latent period. Carcinogens are notorious for such actions, but certain CNS poisons are equally treacherous. Methylmercury is an example. A recent mass outbreak of methylmercury poisoning in Iraq, due to grain treated with a methylmercury fungicide, would have been much more constricted in impact if the effects had not been visible only several weeks after the tainted bread had begun to be eaten [2].

Prenatal exposure is another danger in certain instances. The combination of an immature, developing nervous system with a lack of adequate detoxification mechanisms makes the fetus and neonate especially susceptible. Sometimes, the consequences of such exposure may remain dormant, at least overtly, until the organism reaches a relatively advanced age. Spyker's experiments on prenatal methylmercury exposure [3] indicated that behavioral teratology is a question that embraces the total life span. An adequate screen must confront this set of problems.

Certain aspects of the elementary screen are amenable to easy quantification. Gross locomotor activity can be measured in a variety of ways, some of which are able to distinguish small amplitude movements, such as those associated with tremor, from the large amplitude movements involved in walking and running. Sauerhoff and Michaelson [4] and, also, Silbergeld and Goldberg [5] observed significant increases in the locomotor activity of rodents exposed to lead as neonates.

Other simple measurements can be made with the open field test, which helps an observer gauge an organism's exploratory activity, and which proved useful in Spyker's experiment. She also found swimming tests to be useful for revealing deficits in coordination not discernible in ordinary locomotion. The rotarod, which is simply a rod that revolves at a specified rate, can also be used to test gross coordination. Certain CNS agents impair the ability of rodents to maintain themselves on the rod.

Although body weight often serves as an index of toxic potential, peculiarities in regulatory functions may not be revealed by the usual measures. Suppose, for example, the agent in question destroys hypothalmic tissue. Gross damage may eventually produce hyperphagia and

References

1 Weiss, B., Brozek, J., Hanson, H., Leaf, R.C., Mello, N.K., Spyker, J.M., "Effects on behavior." In The Evaluation of Chemicals for Societal Use, National Academy of Sciences, Washington, D.C (in press).

2 Bakir, F., Damlugi, S.F., Arnin-Zehi, L., Murtadha, M., Khalidi, A., Tikriti, S., Dhahir, H.I., Clarkson, T.W., Smith, J.D., Doherty, R.A., "Methylmercury poisoning in Iraq: an inter-university report," Science, 181, 230 (1973).

3 Spyker, J.M., Sparber, S.B., Goldberg, A.M., "Subtle consequences of methylmercury exposure: behavioral deviations in offspring from treated mothers," Science, 177, 621 (1972).

4 Sauerhoff, M.W., Michaelson, I.A., "Hyperactivity and brain catecholamines in lead-exposed developing rats," Science, 182, 1022 (1973).

5 Silbergeld, E.K., Goldberg, A.M., "A lead-induced behavioral disorder," Life Sci., 13, 1375 (1973).

6 Stebbins, W.C. (Ed.), Animal Psychophysics, Appleton-Century-Crofts, New York (1970).

7 Weiss, B. (Ed.), Digital Computers in the Behavioral Laboratory, Appleton-Century-Crofts, New York (1973).

8 Stebbins, W.C., Miller, J.M., Johnson, L.G., Hawkins, J.E., "Ototoxic hearing loss and cochlear pathology in the monkey," Ann. Otol. Rhinol. Laryngol., 78, 1007 (1969).

9 Falk, J.L., "The behavioral measurement of fine motor control: effects of pharmacological agents," in Thompson, T., Pickens, R., Meisch, R. (Eds.), Readings in Behavioral Pharmacology, Appleton-Century-Crofts, New York (1970).

10 Notterman, J.M., Mintz, D.E., Dynamics of Response, Wiley, New York (1965).

11 Dews, P.B., Herd, J.A., "Behavioral activities and cardiovascular function: effects of hexamethonium on cardiovascular changes during strong sustained static work in rhesus monkeys," J. Pharmacol. Exper. Therap., 189 12 (1974).

12 Laties, V.C., "The modification of drug effects on behavior by external discriminative stimuli," J. Pharmacol. Exper. Therap., 183, 1 (1972).

13 Wood, R.W., Weiss, A.B., Weiss, B., "Hand tremor induced by industrial exposure to inorganic mercury," Arch. Environ. Health, 26, 249 (1973).

14 Laties, V.G., Beard, R.R., Dinman, B.D., Schulte, J.H., "Behavioral effects of carbon monoxide poisoning." In Effects of Chronic Exposure to Low Levels of Carbon Monoxide on Human Health, Behavior and Performance. National Academy of Sciences, Washington, D.C. (1969).

15 Goldberg, D.P., The Detection of Psychiatric Illness by Questionnaire, Oxford University Press, London, England (1972).

16 Parloff, M.B., Kelman, H.C., Frank, J.D., "Comfort, effectiveness and self-awareness as criteria of improvement in psychotherapy," Amer. J. Psychiat, 3, 343 (1954).

DISCUSSION

SANOTSKY (USSR)

In the determination of the threshold of chemical action what is comparative sensitivity of the condition reflex tests or EEG-tests?

WEISS (U.S.A.)

The spontaneous EEG contains much electrical noise; that is, random activity. Only fairly advanced analytical methods, such as Fourier analysis, can make much sense of such information. The availability of the small digital computer, and methods such as the Fast Fourier transform, will help. I am convinced, however, that the evoked potential method because it controls for many more extraneous phenomena, is the method of choice for studies of brain electrical activity. New mathematical methods are also being developed.

As to the comparison you requested behaviorial pharmacology offers cogent evidence for a greater sensitivity of behavioral methods. You can see why, in a behavioral experiment, you can control many extraneous variables, manufacture the behavior to specifications, and measure exactly what you wish.

STEENSBERG (Denmark)

May I draw attention to what was said by Prof. Lawther on the recent colloquium in Luxembourg on carbon monoxide environmental pollution and public health organized by the Commission of the European Communities. In the discussion on perception and performance tests Lawther was giving a warnining to the

c) the problem of pre-testing must be of major concern to scientists: humanity may be exposed to unforeseeable risks unless new chemical products, new processes and new sources of energy are subject, before being used on a large scale, to the most comprehensive possible assessment of the nature and size of the short-, medium- and long-term risks, including the search for any mutagenic, carcinogenic and teratogenic effects and the drawing up of a balance sheet of the advantages and disadvantages for man. A methodological system must be devised which would attempt to forecast the various toxicoligical and ecological risks as accurately as possible, but would also foresee the criteria of purity applicable, the fate of the substances involved in the environment, and methods of detecting them (the product in its pure state, as well as any impurities and metabolites) in the various constituents of the environment;

d) a balance sheet of the advantages and disadvantages for health of the products and techniques employed is essential; however, present approaches are often inadequate in both conception and technique, and the matter must be reconsidered on a multidisciplinary basis. In the same way, it is important to assess more accurately the cost of pollution and pollution control as well as the effectiveness of control methods and their possible secondary effects on health. This knowledge will be used, together with other socio-economical and regional elements, in the process of making decisions starting from criteria and aiming at quality objectives and standards.

In this connection, particular attention should be paid to the problems of developing countries thus, the need for development might take precedence over the need for protection.

4. Alongside clear or more-or-less easily identifiable symptoms, changes regarded as infra-pathological or difficult to interpret, like mitochondrial enzyme stimulation or modifications of delta-aminolevulinic acid dehydratase in persons exposed to lead, are often observed. Research is needed to enable us to interpret these changes more accurately and to know whether they are just concomitants or subtle impairments preceding outright pathological symptoms: it would also be useful to know whether these changes may be used as indicators of exposure.

5. In connection with the preceding point, the following problems arise:

a) the choice of critical groups to be taken into consideration from the health point of view, and of the extent of any risks which might reasonably be accepted for these groups;

b) the choice of priorities in scientific research, based in particular on knowledge of the nature of the risk, its extent and reversibility, and of the possibilities for action, both for natural pollutants and those originating in human activity.

6. Similarly, we must consider in a different light risks observed in normal conditions and accidental risks: the acceptable limits for the latter must be derived from criteria applied to acute exposure and appropriate counter measures must be in proportion to the extent of the danger and the number of individuals threatened.

7. Regarding the values currently accepted as standards there is no doubt that some of them must be revised in the light of present knowledge; this is particularly the case for certain maximum allowable concentrations at work places. Certain long-term effects have not been taken sufficiently into consideration, perhaps because not enough attention has been paid to the fact that occupational exposure is increased by non-occupational exposure, and above all because it has sometimes been over looked that more and more women capable of child-bearing are working in industry: certain values must unquestionably be rethought and account must be taken of transplacental and transmammary transfers and of the protection of foetuses and breast-fed children.

We gave a definition of the term "criterion" at the beginning of this paper. Before considering certain fundamental studies the significance of which was stressed during the discussions, we should like to draw our colleagues' attention to three points which seem important to use:

1. Firstly, some exposures effects like odours or certain kinds of noises tend to take the form of annoyances; although it is not possible to calculate these exposures nor to quantify their effects. A judgement on criteria could nevertheless be made, enabling the decision making process to be set in motion. This does not mean that technical and methodological efforts should not be made to evolve numerical data as soon as possible.

2. It is also necessary to stress that in certain cases decisions must be taken regarding the setting of standards or reference values, or the introduction of regulations, before the criteria can be finally established; in such cases it is necessary to collect as much scientific data as possible, and these may even be incomplete or analogical, as long as they are clear enough to support the decisions made. Such data must be confirmed experimentally or epidemiologically as quickly as possible.

3. Finally, there is a need to pursue experimental and clinical research, for example a more effective evaluation of the psychological effects of certain nuisances and stresses of modern living, and a better knowledge of the psychological effects of certain nuisances (equivalent to the biological effects of noise)

Nous avons trouvé dans la présence de Mme Veil, Ministre français de la Santé, un témoignage dont le congrès peut être particulièrement fier et heureux. Je voudrais sur ce point particulier, au nom du Symposium, remercier le Gouvernement français de nous avoir délégué pour présider la séance d'ouverture la personnalité officielle qui par vocation et par fonction a pour tâche de protéger la santé humaine. Si, comme j'ai eu l'occasion de le dire lors de la table ronde, il faut appliquer à l'environnement les concepts et les méthodes de la médecine, cela ne signifie pas pour autant que l'environnement soit essentiellement un problème médical. Les sciences de l'environnement ressortissent à de nombreuses disciplines qui cherchent actuellement à s'entendre et à se concerter, dans un souci d'économie et d'efficacité.

A cet égard, le Symposium est une réussite car avec la participation de 800 délégués, représentant aussi bien les sciences fondamentales que la médecine clinique, la toxicologie et l'écologie, nous avons pu jeter les bases d'un accord et dégager des objectifs communs, malgre certaines lacunes et imperfections que Monsieur Lafontaine vient de nous présenter.

Lors de la conférence de presse de ce matin, nous avons eu l'occasion de dire que jamais la science ne s'est trouvée devant une telle responsabilité et que jamais le rôle moral qu'elle doit jouer n'a été aussi important et lourd de conséquences pour l'avenir de l'homme.

Il n'est pas possible d'étudier les problèmes qui sont posés en oubliant les buts auxquels nous devons tendre et qui doivent nous servir de point d'accrochage pour nos entreprises et nos réflexions. Certes, nous devons accepter de concéder à la technique la part suffisante qui lui revient, en vue de la développer et d'en harmoniser les performances, mais nous devons orienter le développement de la technologie dans la mesure où elle est indispensable à réaliser l'objectif gereral de qualite de vie que nous nous sommes assignés.

La prise de conscience de l'importance de l'environnement est récente et dans certains cas elle a été dramatique. La révélation du nombre de problèmes à résoudre, la quantité considérable de matières à étudier et qui se sont entassées ces dernières années devant les chercheurs et les responsables politiques sont tels qu'un certain désarroi et un certain désordre sont apparus dans les milieux qui veulent promouvoir le bonheur de l'humanité et améliorer la qualité de la vie.

Je crois que le Symposium qui vient de se terminer a permis d'opérer une certaine classification dans les problèmes posés, d'établir des priorités et surtout de donner leur véritable dimension à des préoccupations dont le monde entier est conscient, en soulignant les questions urgentes et en dédramatisant des problemes mal posés.

Nous pouvons nous demander quel est l'enjeu de la lutte contre les pollutions. Cet enjeu est immense mais il est certain qu'il dépasse le cadre d'une génération et que parmi les grands problèmes à résoudre il y a une meilleure connaissance des effets lointains des pollutions, y compris les effets héréditaires, alors que, sauf pour les radiations ionisantes, la plupart des éléments polluants du milieu ne sont étudiés que dans les perspectives d'une action potentielle de quelques années.

Il y a dans l'extraordinaire aventure collective où nous nous engageons, deux objectifs qui paraissent contradictoires. Il y a d'une part la promotion de la qualité de la vie individuelle, à laquelle nous sommes tous personnellement attachés et d'autre part, le développement d'un type de société particulièrement efficace mais qui met en danger l'individu et ses aspirations profondes. Cette contradiction entre l'efficacité de la société et la recherche du bonheur individuel est déroutante et doit nous conduire à nous poser une série de questions et à tenter de les résoudre.

De tels problèmes ne sont pas uniquement du ressort de la philosophie. Nous devons en tant qu'homme ministrateurs de la santé prendre conscience de la complexité des points d'interrogation et leur appliquer la méthode scientifique dont ce congrès a démontré la valeur et l'irremplaçable mission de conseil et d'inspiration politique.

Le hasard a voulu que notre Symposium se tienne à Paris, dans ce pays où sont nés la méthode expérimentale et le raisonnement scientifique, et ce n'est pas sans motif que l'un des participants a fait allusion à Claude Bernard et à l'oeuvre qui l'a immortalisé. Mais il faut que nous soyons honnêtes avec nous-mêmes et que nous n'attribuons pas à la science plus qu'elle ne peut et ne doit accepter. Si son rôle est d'aider, en analysant et en objectivant les phénomènes scientifiques, les autorités qui doivent prendre des décisions, elle ne peut se substituer à ces dernières pour transférer sur le plan de la réglementation ou de la politique les résultats des constatations scientifiques.

La conférence de presse que nous avons tenue ce matin et qui a été suivie avec beaucoup d'intérêt par un grand nombre de journalistes, indique que la presse entend jouer le rôle qui lui revient dans l'information objective du public et dans la mobilisation de l'opinion en faveur de la défense et de la protection de l'environnement.

Il est particulièrement favorable que nous ayons pu, au cours de ces cinq journées, en toute objectivité et en toute franchise, avec les portes largement ouvertes vers l'extérieur, présenter un bilan positif souvent et négatif parfois, de l'état de nos connaissances, et indiquer les grandes lignes et les orientations d'une action en faveur de l'environnement et de la santé humaine.

Ce Symposium a suscité une espérance pour l'avenir de nos sociétés humaines mais il a aussi prouvé que les chercheurs et les responsables de la santé et de l'environnement possèdent l'indépendance et la liberté d'esprit qui sont toujours les conditions essentielles au progrès de l'humanité.

CONCLUDING REMARKS *(translation)*

DR. P. RECHT
Director for Health Protection,
Commission of the European Communities
Luxembourg (Grand Duchy)

Having reached the end of this symposium, a strenuous one for organizers and participants alike in view of the wide-ranging subject matter, the tight schedule of sessions, the large number of reports and papers and the intensity of the discussions, we all no doubt have many comments to make. Those who have already spoken have summed up admirably the reactions and comments which this gathering has certainly evoked.

As the last speaker, I should like, on behalf of the Commission of the European Communities, to endorse the opinions which have just been expressed by my two colleagues and friends of the World Health Organization and of the United States Environmental Protection Agency. I agree wholeheartedly with their views and should like to add that in organizing this conference we have laid the foundation for an effective tripartite collaboration which will certainly prove its worth in the future.

The difficulties inherent in this symposium became apparent as soon as the organizing committee and the scientific advisers began to sift the large number of reports and papers submitted, with a view to selecting the most appropriate.

By their very diversity the papers presented over the past five days have clearly illustrated the many-sided and complex character of environmental problems, and thus the need to develop a common methodological approach to tackle them.

Despite the positive results obtained, it is certain that scientifically valid solutions have yet to be achieved in very many fields. This remark is not intended as a criticism of scientific research in the environmental field, but as an encouragement, dear Dr. Dietrich, to ask W.H.O. to intensify its activities still further, and to play a vital role in the establishment of common health criteria and standards. It is time that the protection of man and his living environment was given its proper place in environmental studies, and be tackled by those competent and responsible for doing so.

We have been particularly honoured and gratified by the presence here of Mrs Veil, the French Minister of Health. On behalf of all those who have attended this symposium I should like to thank the French Government for having delegated Mrs Veil, who both professionally and in her official capacity has the task of protecting human health, to preside over our opening session. Although, as I had occasion to say during the round-table discussion, medical concepts and methods must be applied to the environment, this does not mean that the environment is essentially a medical problem. Environmental sciences embrace a wide range of disciplines, which are at present endeavouring to work together in closer harmony in the interests of economy and efficiency.

In this respect the symposium has been a success because, with 800 delegates representing not only the fundamental sciences but also clinical medicine, toxicology and ecology, we have been able to find common ground and establish common objectives, despite the gaps and imperfections to which Dr. Lafontaine has just referred.

At this morning's press conference we said that science had never before had to carry such a great responsibility, and that its moral role had never been so important and fraught with consequences for man's future. When examining the problems facing us we must always keep clearly in mind the goals we are aiming at, for it is these which must guide our thinking and our action. Technology must, of course, be allowed its proper role, and must be developed and its results harmonized, but its development must depend on the degree to which it can help us achieve our overall goal of improving the quality of life.

The general awareness of the crucial importance of the environment is recent, and in some cases has come dramatically. The realization of the enormous number of problems to be solved and fields to be studied by research workers and politicians has caused a certain amount of confusion and disarray among those who aim to promote human happiness and improve the quality of life.

I feel that the symposium which has just ended has enabled us to some extent to sort out the problems facing us, to establish priorities and above all to put in their proper perspective the problems which are troubling the world, emphasizing the urgent ones and stripping the less important ones of their sensationalist aspects.

We must think about what is at stake in our struggle against pollution. There is, of course, and immense amount at stake, but it is certainly not confined to one generation: one of the major problems confronting us is how to improve our knowledge of the long-term and hereditary effects of pollution, since, except in the case of ionizing radiation, most pollutants have been studied solely with a view to their possible effects over periods of a few years.

In the extraordinary adventure in which we are all engaged there are two apparently contradictory objectives. On the one hand we wish to improve the individual's quality of life, - this concerns us all personally - and on the other we seek to develop a highly efficient society, which threatens the individual and his most profound aspirations. This contradiction between the efficiency of society and the search for individual happiness is disturbing, and should cause us to ask ourselves a number of questions, and try to answer them.

Such questions are not confined to the realms of philosophy. As scientists and health administrators we must be aware of the complexity of the problems facing us and apply scientific methods in solving them. This symposium has shown these methods to be of irreplacable value as sources of guidance and political inspiration.

Chance has ordined that our symposium should be held in Paris, in this country which is the home of experimental methods and scientific reasoning, and it is significant that one participant alluded to Claude Bernard and the work which immortalized him. But we should be honest with ourselves and not ask of science what it cannot, indeed may not, give. While those who have to make decisions should be assisted by the objective analysis of scientific phenomena, the results of scientific observations must not become the all-important factors in legislative and political decisions.

This morning's press conference, which aroused much interest and which was attended by a large number of journalists, indicated that the press intends to fulfill its role of providing objective information and of educating public opinion in favour of environmental protection.

We have been particularly fortunate over the past five days in being able, frankly and with complete objectivity, and with our doors wide open to the outside world, to discuss the frequently positive and sometimes negative aspects of our knowledge and to outline the programmes which will have to be introduced to protect the environment and human health.

This symposium has given us fresh hope in the future of our societies but it has also proved that research workers and those responsible for health and the environment possess the independence and freedom of mind which are always the essential prerequisite for human progress.

2469

TEILNEHMERLISTE

LIST OF PARTICIPANTS

LISTE DES PARTICIPANTS

LISTA DEI PARTECIPANTI

LIJST VAN DE DEELNEMERS

Preceding page blank

ARGENTINA

BENINSON D.
Gerencia de Proteccion
Radiologica y Seguridad
Buenos Aires 29

AUSTRALIA

ALLAN A.
Mount ISA Mines Ltd.
Mount ISA
Queensland 4825

JOHNSON H. M.
Broken Hill Associated Smelters
Box 219, Port Pirie
South Australia 5540

MICHAUX E.
Health Service
21 Rokeby Terrace
Taringa 4068
Brisbane, Queensland

SHEPHERD W.
C.S.I.R.O.
Division of Atmospheric
Physics
Station Street
Aspendale, Victoria

BELGIË / BELGIQUE

BORMANS M. J. J.
Fédération des Industries
Chimiques, ECOCHEM
49 Square Marie Louise
1040 Bruxelles

BOUQUIAUX J. J.
Institut d'Hygiène et
d'Epidémiologie
14 rue Juliette Wytsman
1050 Bruxelles

BRUAUX P.
Institut d'Hygiène et
d'Epidémiologie
14 rue Juliette Wytsman
1050 Bruxelles

BUCHET J.-P.
Unité de Toxicologie Industrielle et Médicale
Université Catholique de Louvain
Avenue Chapelle aux Champs 4
1200 Bruxelles

COFFIELD T. H.
Ethyl S.A.
1 rue Paul Lauters
1050 Bruxelles

DAMS R.
Instituut voor Nucleaire
Wetenschappen
Rijksuniversiteit Gent
Proeftuinstraat 86
9000 Gent

DEMARET Y.
Groupement International
des Associations Nationales
de Fabricants de Pesticides
28 Square Marie Louise
1040 Bruxelles

DE MEULEMEESTER A.
Texaco Services (Europe) Ltd.
31 Pres. J. F. Kennedylaan
9020 Gent

Preceding page blank

LINDELL K.
Institute of Occupational
and Environmental Health
R.R.4., Danville
Quebec JOA 1A0

LISTON A. J.
Environmental Health
Directorate
Department of National
Health and Welfare
Ottawa, Ontario K1A 0L2

LORENZI L.
588 Barton Street E.
Hamilton, Ontario

MONKMAN J. L.
Air Pollution Control
Directorate
Environmental Health Centre
Tunney's Pasture
Ottawa, Ontario K1A 0H3

NEWHOUSE M.
McMaster University
St. Joseph's Hospital
Hamilton, Ontario

OLOFFS P. C.
Department of Biological
Sciences
Simon Fraser University
Burnaby 2, B.C.

PICHE L.
Université de Montréal
Département de Chimie
Montréal 101, Québec H3C 3V1

SMITH D. M.
Gouvernement du Canada
Ministère de la Santé et
du Bien-Etre Social
Services Internationaux
d'Hygiène
Ottawa, Ontario K1A 0K9

STOPPS G. J.
Ministry of Health
Province of Ontario
15 Overlea Boulevard
Toronto, Ontario

WIEBE A.
Atmospheric Environment
Service
Department of Environment
4905 Dufferin Street
Downsview, Ontario M3H 5T4

ZERBE H.
640 Boulevard Graham
Ville Mont Royal
Québec

CITTA' DEL VATICANO

DUBARBE D.
Nonciature Apostolique
72 Avenue de Tervuren
Bruxelles, Belgique

SATRA J.
Nonciature Apostolique
72 Avenue de Tervuren
Bruxelles, Belgique

C.S.S.R.

PELECH L.
Institute of Postgraduate
Training for Physicians
and Pharmacists
Bratislava

PFEIFER I.
Czechoslovak Research and
Development Centre for
Environmental Pollution
Control
100 42 Praha 10
Srobafova 48

ROSIVAL L.
Research Institute of Hygiene
Bratislava
Ul.Cs.armády 40

SCHMIDT P.
Institute of Hygiene and Epidemiology
Centre of General and Environmental Hygiene
100 42 Praha 10
Srobafova 48

STEPANEK V.
Czechoslovak Research and Development Centre for Environmental Pollution Control
120 00 Praha 2

SYMON K.
Institute of Hygiene and Epidemiology
Centre of General and Environmental Hygiene
100 42 Praha 10
Srobafova 48

DANMARK

CARSTENSEN J.
National Food Institute
Institute of Toxicology
Mørkhøjgaard
19 Mørkhøj Bygade
2860 Søborg

FAKSTORP J.
F. L. Smidth & Co. A/S
Environmental Technology Division
Gl. Koege Landevej 55
2500 Valby

FLYGER H.
Danish Atomic Energy Commission
Research Establishment
Risø
4000 Roskilde

FUNCH-ENGBERG A.
National Food Institute
Institute of Toxicology
Mørkhøjgaard
19 Mørkhøj Bygade
2860 Søborg

HANSEN J. C.
Institute of Hygiene
University of Aarhus
Universitetsparken
8000 Aarhus C

MAGE D.
Laboratoriet for Varme- og Klimateknik
Danmarks Tekniske Høskole
Bygning 402
2800 Lyngby

STEENSBERG J.
Ministry of the Environment
Agency of Environmental Protection
47 Store Kongensgade
1264 Copenhagen K

UHL E.
Sundhedsstyrelsen
St. Kongensgade 1
1264 Copenhagen K

DEUTSCHE DEMOKRATISCHE REPUBLIK

HORN K.
Ministerium für Gesundheitswesen
102 Berlin
Rathausstr. 3

EGYPT

ATTIA M.
Ministry of Health
Cairo

EL-SHEBOKSHY A.
Ministry of Health
Cairo

FARAG S. A.
Air Pollution Unit
National Research Center
Dokki, Cairo

MASSOUD A.
Department of Industrial Medicine
Cairo University
Faculty of Medicine
14 Gezira Street
Zamalek Cairo

FRANCE

ALARY R. S. E.
Laboratoire Central de la Préfecture de Police
39 bis rue de Dantzig
75015 Paris

ALQUIER J. P.
Laboratoire Central de la Préfecture de Police
39 bis rue de Dantzig
75015 Paris

ALVINERIE R. M.
Institut National de la Recherche Agronomique
180 chemin de Tournefeuille
31300 Toulouse

ANDREUX J.-P.
Hôpital Boucicaut
78 rue de la Convention
75015 Paris

ARSAC F.
Faculté de Pharmacie
Laboratoire de Toxicologie
rue J. B. Clément
92290 Chatenay-Malabry

AUBERT M.
C.E.R.B.O.M.-I.N.S.E.R.M.
Parc de la Côte
1 avenue Jean Lorrain
06300 Nice

AUDRAN R.
Institut National de Recherche et de Sécurité
30 rue Olivier Noyer
75680 Paris Cedex 14

BEAU P.
Commissariat à l'Energie Atomique
Boîte Postale 6
92260 Fontenay-aux-Roses

BENARIE M.
I.R.C.H.A.
Boîte Postale 1
91710 Vert-le-Petit

BENET M.
Société Languedocienne de Soufre et Micron-Couleurs
A.P.C. S.A.
Boîte Postale 79
11102 Narbonne

BERTIN M.
Electricité-Gaz de France
30 avenue Wagram
75008 Paris

BIGNON J.
Clinique de Pneumo-Phtisiologie
Hôpital Laennec
42 rue de Sèvres
75007 Paris

BITTEL R.
Commissariat à l'Energie Atomique
Département de Protection
Boîte Postale 6
92260 Fontenay-aux-Roses

BLAKE M.
Centre Universitaire de Savoie
Laboratoire de Zoologie et Biologie
Boîte Postale 143
73011 Chambéry

BLANCHER G. L. G.
Faculté de Médecine de Paris (Ouest)
1 rue de l'Université
75007 Paris

BOISVIEUX
Société Antar
4 rue Léon Jost
75017 Paris

BONNEFOUS
Association National de l'Environnement
18 rue Duphot
Paris

BORDET F.
Elf-Union
12 rue Jean Micot
75340 Paris Cedex 07

BOUDENE C.
I.N.S.E.R.M., U.122
Université Paris-Sud
rue Jean Baptiste Clément
92290 Chatenay-Malabry

BOURDEIX J.
74 Cours Lafayette
69003 Lyon

BOURGEOIS R.
La Presse Française
64 rue de Rome
75008 Paris

BOVARD P.
Commissariat à l'Energie Atomique
Département de Protection
Boîte Postale 6
92260 Fontenay-aux-Roses

BOYD S.
Sierra Club
24 avenue Charles Floquet
75007 Paris

BRESSION H.
Préfecture de Paris
Laboratoire d'Hygiène
1 bis rue des Hospitalières St. Gervais
75004 Paris

BRESSON G.
Commissariat à l'Energie Atomique
Département de Protection
Boîte Postale 6
92260 Fontenay-aux-Roses

BRILLE D.
Institut National de la Santé et de la Recherche Médicale
184 rue du Faubourg St. Antoine
75012 Paris

CABANE E.
Ciba-Geigy S.A.
2 - 4 rue Lionel Terray
92505 Rueil Malmaise

CABRIDENC R.
Institut de Recherche Chimique Appliquée
Boîte Postale 1
91000 Vert-le-Petit

CAILLARD L.
Société Rhône-Poulenc
21 rue Jean Goujon
75008 Paris

CASANOVA H. P.
I.N.R.A.
Route de St. Cyr
78000 Versailles

CHAMBON P.
Laboratoire de Toxicologie et Hygiène Industrielle
Faculté Mixte de Médecine et Pharmacie
8 avenue Rockefeller
69008 Lyon

CHANSON
Société Antar
4 rue Léon Jost
75017 Paris

CHANTEUR J.
Ministère de la Santé Publique
et de la Securité Sociale
78110 Le Vésinet

CHAPOUX E.
Union Technique de l'Automobile, du Motocycle et du
Cycle (UTAC)
157 rue Lecourbe
75015 Paris

CHAUVEAU J.
Institut de Recherches
Scientifiques sur le
Cancer
Boîte Postale 8
94800 Villejuif

CHEMINAT J. C.
Hôpital Sabourin
Boîte Postale 12
63018 Clermont-Ferrand

CHESNAIS J. C.
I.N.E.D., C.N.R.S.
Bureau 316
27 rue du Commandeur
75675 Paris-Cedex 14

CHEVRIER M.
Régie Nationale des
Usines Renault
Direction des Laboratoires
Boîte Postale 103
92109 Boulogne Billancourt

CHOVIN P.
Laboratoire Central de la
Préfecture de Police
39 bis rue de Dantzig
75015 Paris

CICOLELLA A.
I.N.R.S.
route de Neufchâteau
54500 Vandoeuvre

CLAUDE J. R.
Laboratoire de la
Préfecture de Paris
88 rue de la Jonquière
75017 Paris

COHEN M.
Hygiène Industrielle
Esso S.A.F.
92080 Paris la Défense
Cedex 2

COIN L.
Boîte Postale 42
94220 Charenton

CONSO F.
Hôpital Fernand Widal
Clinique Toxicologique
200 rue Fbg St. Denis
75010 Paris

CORTIER J.
Ciba-Geigy S.A.
2 - 4 rue Lionel Terray
92505 Rueil Malmaise

COSSON G.
Pharmacie de l'Hôpital
Broussais à Paris
110 due Pierre Brossolette
(P. Corby)
92320 Chatillon

COULON
Picheney Ugine Kuhlmann
23 rue Balzac
75008 Paris

COURGIBET G.
Régie Nationale des
Usines Renault
Direction des Laboratoires
Boîte Postale 103
92109 Boulogne Billancourt

COUTEAUX H.
Société Nationale des
Pétroles d'Aquitaine
26 avenue des Lilas
64000 Pau

CUMONT G.
Ministère de l'Agriculture
Direction des Services
Vétérinaires
Laboratoire Central
d'Hygiène Alimentaire
43 rue de Dantzig
75015 Paris

DANA V.
Management Science Operations Research
36 rue Claude Decaen
75012 Paris

DANIEL H.
CERCHAR
Boîte Postale 27
60103 Creil

DAVOUST P.
Institut Universitaire de Lorient
Département d'Hygiène et de Sécurité
rue de Londres
56100 Lorient

DECLOÎTRE F.
Institut de Recherches Scientifiques sur le Cancer
Boîte Postale 8
94800 Villejuif

DEIT N.
Revue Technique Internationale de l'Eau
9 rue Coetlogon
75006 Paris

DELAMAIN J.
Ministère de l'Environnement
13 rue de Bourgogne
75007 Paris

DE LAVOUR
I.N.R.A.
Laboratoire de Phytopharmacie
C.N.R.A. route de St.Cyr
78000 Versailles

DELPLA M.
Electricité de France
Comité de Radioprotection
3 rue de Messine
75008 Paris

DELSEY J.
Institut de Recherche des Transports
Centre d'Evaluation et de Recherche des Nuisances
109 Chemin St. Jean
69000 Bron

DESBORDES J.
Pr. Centre Hospitalier
76600 Le Havre

DETRIE J. P.
Centre Interprofessionnel Technique d'Etudes de la Pollution Atmosphérique
28 rue de la Source
75016 Paris

DUBOIS G. J.
Faculté de Médecine
3 Allée des Piquiers
59700 Lille

DUCHESNE M. C.
Ministère de l'Agriculture
Service de la Répression des fraudes et contrôle de la qualité
42 bis rue de Bourgogne
75007 Paris

DUPUIS P. J.
39 Parc du Val d'Or
92210 St. Cloud

EFTHYMIOU M. L.
Hôpital Fernand Widal
200 rue du Faubourg St Denis
75475 Paris-Cedex 10

ESCOULA L. G.
Institut National de la Recherche Agronomique
180 chemin de Tournefeuille
31 Saint Martin du Touch

FABRE M.
Laboratoire d'Hygiène de la Ville de Paris
1 bis rue des Hospitalières St. Gervais
75004 Paris

FARGES L. F. P.
Commissariat à l'Energie Atomique
Boîte Postale 6
92260 Fontenay-aux-Roses

FAUDEMAY F.
I.N.S.E.R.M.
78 avenue de Suffren
75007 Paris

FAUGERE J. G.
Laboratoire Municipal
rue du Professeur Vèzes
33000 Bordeaux

FESTY B.
Laboratoire d'Hygiène
1 bis rue des Hospitalières
St. Gervais
75004 Paris

FONDIMARE A. H. P.
Lab. d'Analyses Path.
76600 Le Havre

FONTVIEILLE D. A. J.
Centre Universitaire de
Savoie
Laboratoire de Zoologie
et de Chimie
Boîte Postale 143
73011 Chambéry

FOURNIER E.
Hôpital Fernand Widal
200 rue Fbg St. Denis
75010 Paris

FROC J.
Institut National de
Recherches Agronomiques
C.N.R.A. Rte de St. Cyr
78000 Versailles

GALTIER P. E.
Institut National de la
Recherche Agronomique
180 Chemin de Tournefeuille
31300 Toulouse

GARNIER
SPS/PE
Département de Protection
Centre d'Etudes Nucléaires
Boîte Postale 6
92260 Fontenay-aux-Roses

GARREL P. M.
Société de Médecine du
Travail
37 rue du Départ
75014 Paris

GAUDIN G. J. L.
Secrétariat Général de la
Défense Nationale
51 bd de Latour Maubourg
75007 Paris

GERIN-ROZE C. M. M.
Laboratoire d'Hygiène de
la Ville de Paris
1 bis rue des Hospitalières
St. Gervais
75004 Paris

GILLES G.
Laboratoire des Services
Vétérinaires
66 rue St. Sébastien
13252 Marseille Cedex 2

GILLON J. J.
Revue le Concours Médical
37 rue de Bellefosse
75009 Paris

GIRARD-WALLON C.
Université Paris VI. UER
Broussais, Hôtel Dieu
185 avenue Aristide Briand
94230 Cachan

GODIN J.
I.N.S.E.R.M., U.122
Laboratoire de Toxicologie
Faculté de Pharmacie
rue J. B. Clément
92290 Chatenay-Malabry

GRADISKI D.
I.N.R.S.
route de Neufchâteau
54500 Vandoeuvre

GRIFFATON G.
Institut National de la
Santé et de la Recherche
Médicale
Laboratoire de Nutrition
Humaine
Hôpital Bichat
170 boulevard Ney
75018 Paris

GRISONI S.
Laboratoire d'Hygiène de la
Ville de Paris
1 bis rue des Hospitalières
St. Gervais
75004 Paris

GROS R.
Commissariat à l'Energie
Atomique
10 Allée Jacques Cartier
91430 Igny

GUERIN M.
Société Française de Pétrole
B.P.
10 quai Paul Doumer
92 Courbevoie

GUIBKY M. T.
14 rue Juliette Lamer
75017 Paris

HALPERN J.
I.N.S.E.R.M.
Centre de Documentation
Hôpital de Bicêtre
94270 Le Kremlin-Bicêtre

HEDDE L. M.
Société Octel
8 rue Bellini
75782 Paris Cedex 16

HENRY G.
Association Française des
Femmes Médecins
65 boulevard Garibaldi
75015 Paris

HO M. T.
I.N.R.S.
route de Neufchâteau
54500 Vandoeuvre

HUBERT-HABART M. A.
Fondation Curie
Institut de Radium
26 rue d'Ulm
75005 Paris

JARRY J. J.
Institut National de
Recherche et de Sécurité
30 rue Olivier Noyer
75680 Paris Cedex 14

JEANMAIRE L.
Commissariat à l'Energie
Atomique
Département de Protection
Boîte Postale 6
92260 Fontenay-aux-Roses

JUGUET B. E. E. O.
Laboratoire d'Hygiène
1 bis rue des Hospitalières
St. Gervais
75004 Paris

KAUFFMANN F.
I.N.S.E.R.M., U. 68
Hôpital Saint Antoine
75571 Paris Cedex XII

LABONDE J.
Laboratoire d'Hygiène
1 bis rue des Hospitalières
St. Gervais
75004 Paris

LAMBOTTE J.
Ministère de l'Environnement
Direction de la Prévention
des Pollutions et Nuisances
13 rue de Bourgogne
75007 Paris

LAREDO N.
Comité Anti-Pollution
Boues Rouges
66 boulevard Jean Jaurès
94000 Fresnes

LECLERC F.
Hôpital Broussais
96 rue Didot
75014 Paris

LECLERC J.-L.
Laboratoire Central de la
Préfecture de Police
39 bis rue de Dantzig
75015 Paris

LECLERC M.
Hôpital Broussais
96 rue Didot
75014 Paris

LECLERC P. P. M.
Service de Pneumologie
Hôtel Dieu
160 rue Blomet
75015 Paris

LE COADIC Y.
Institut Universitaire de
Lorient
Département Hygiène et
Sécurité
rue de Londres
56100 Lorient

ITALIA

ALBERTONI F.
Istituto di Tisiologia
II Catt. Università di
Roma
Via Baldassarre Peruzzi 6
00153 Roma

ALESSIO L.
Clinica del Lavoro
Via S. Barnaba 8
20122 Milano

BARRO G.
Regione dell'Umbria
Via. S. Bonaventura, 10
06100 Perugia

BERETTA F.
Clinica del Lavoro
Via M. Greppi 10
20135 Milano

BIANCO A.
Laboratorio Radioattività
Ambientale C.N.E.N.
C.S.N. Casaccia, C.P. 2400
00100 Roma

BONAZZI G.
Università Parma
Laboratorio di Ecologia
Borgo Carissimi 10
43100 Parma

CACCURI S.
Istituto di Medicina del
Lavoro dell' Università
Policlinico
Piazza Miraglia
80130 Napoli

CASTELLINO N.
Medicina Lavoro
Università Napoli
Via Raffaele de Cesare 31
80132 Napoli

CASULA D.
Istituto di Medicina del
Lavoro dell'Università
degli Studi di Cagliari
Via S. Giorgio 12
09100 Cagliari

CASULE G.
Regione Toscana
Piazza Libertà 15
50129 Firenze

CERQUIGLINI-MONTERIOLO S.
Istituto Superiore di
Sanità
Viale Regina Elena 299
00161 Roma

CLEMENTE G. F.
Laboratorio Radioattività
Ambientale C.N.E.N.
C.S.N. Casaccia
C.P. 2400
00100 Roma

COLOMBINI M.
Ministero della Sanità
Via Liszt 34
00100 Roma

CONENNA C.
"Italia Nostra"
Piazza Fontane Marose 6/5
16123 Genova

COTTA-RAMUSINO F.
Istituto Superiore di
Sanità
Viale Regina Elena 299
00161 Roma

DEL BORGHI M.
Istituto di Scienze e Tecnologie dell'Ingegneria
Chimica
Facoltà di Ingegneria
Via all'Opera Pia 11
16145 Genova

FADDA F.
Enti locali ecologia
urbanistica
Regione Sarda
09100 Cagliari

FAILLACE R.
Regione Toscana
c/o Dip. Sicurezza Sociale
Piazza della Libertà 15
50129 Firenze

FAVRETTO L.
Istituto di Merceologia
Università di Trieste
34100 Trieste

FILASTO-NARESE M.
Regione Toscana
Dipartimento sicurezza sociale
Piazza della Libertà 15
50129 Firenze

GADONI S.
Enti locali ecologia urbanistica
Regione Sarda
09100 Cagliari

GARIBALDI P.
Snam Progetti
20097 S.Donato Milanese
Milano

GARLANDA T.
Montedison S.p.A.
Via Turati 7
20121 Milano

GATTI G. L.
Istituto Superiore di Sanità
Viale Regina Elena 299
00161 Roma

GHETTI P. F.
Laboratorio di Ecologia
Università di Parma
Strada Università 12
43100 Parma

GRASSO C.
Università degli Studi di Firenze
Istituto di Igiene
Viale G. B. Morgagni 48
50134 Firenze

LA FORGIA M.
Assessorato all'Igiene e alla Tutela dell'Ambiente
Regione Emilia-Romagna-Bologna
Viale Silvani 6
40122 Bologna

LANZOLA E.
Istituto di Igiene dell'Università
Viale Forlanini 1
27100 Pavia

MAGI F.
E.N.I.
P.le Enrico Mattei 1
00144 Roma

MARINI G.
Enti locali ecologia urbanistica
Regione Sarda
09100 Cagliari

MARRACINI A.
Enti locali ecologia urbanistica
Regione Sarda
09100 Cagliari

MONTEROSSO M.
Regione dell'Umbria
Via S. Bonaventura 10
06100 Perugia

NARESE C.
via Rondinelli 2
50123 Firenze

PALMAS A.
Enti locali ecologia urbanistica
Regione Sarda
09100 Cagliari

PASQUINI R.
Istituto d'Igiene dell'Università degli Studi di Perugia
Via del Giochetto
06100 Perugia

PECORA L.
Istituto di Medicina del Lavoro
Università Napoli
Via Schipa 61
80122 Napoli

PERTOSA M.
Istituto d'Igiene dell'
Università degli Studi
di Perugia
Via del Giochetto
06100 Perugia

SACCHETTI A.
Assessorato all'Igiene e
alla Tutela dell'Ambiente
Regione Emilia-Romagna-
Bologna
Viale Silvani 6
40122 Bologna

SANTARONI G.
Istituto Nazionale della
Nutrizione
Città Universitaria
00161 Roma

SANTI L.
Istituto di Oncologia
dell'Università di Genova
Viale Benedetto XV
16132 Genova

SAVINO A.
Istituto d'Igiene dell'
Università degli Studi
di Perugia
Via del Giochetto
06100 Perugia

SCASSELLATI SFORZOLINI G.
Istituto d'Igiene dell'
Università degli Studi
di Perugia
Via del Giochetto
06100 Perugia

SEMIANI P. L.
E.N.I.
Piazzale E. Mattei 1
00144 Roma

SENNI L.
Tecneco S.p.A.
(E.N.I.)
C.P. 47
Fano (P.S.)

SIRIGU M.
Enti locali ecologia
urbanistica
Regione Sarda
09100 Cagliari

VANINI G.
Istituto di Igiene
dell'Università Torino
Via Santena 5 bis
Torino

VIVOLI G.
Istituto di Igiene
Università di Modena
Via Campi 287
41100 Modena

JAPAN

GOTO M.
Laboratory of Ecological
Chemistry
Faculty of Science
Gakushuin University
Toshima-Ku
Tokyo 171

ISAO U.
Environmental Health Sec-
tion of Osaka Fu Gov.
25-1 Otemae no Cho
Higashi Ku
Osaka

KABURAGI K.
Mitsubishi Metal Corporation
5-2 Ohte-Machi 1-Chome
Chiyoda-Ku
Tokyo 100

KAWAI K.
National Institute of
Industrial Health
221 Kizuki-Sumiyoshi-Cho
Kawasaki

TAGUCHI S.
Department of Physiology
School of Life Science
Rissho Women's University
3337 Minamiogishima
Koshigaya-shi
Saitama

TAKENAKA K.
Environment Agency
3-1-1 Kasumigaseki
Chiyoda-ku
Tokyo

TATI M.
Department of Public
Health
Gifu University
School of Medicine
Tsukasa-maci 40
Gifu

TOMITA K.
Public Nuisance and Medical
Research Institute, Inc.
c/o Mitsui Mining & Smelting Co., Ltd.
2-1-1 Nihonbashi-Muromachi
Chuo-Ku
Tokyo

TSUCHIYA K.
Department of Preventive
Medicine & Public Health
School of Medicine
Keio University
35 Shinanomachi
Shinjuku-Ku
Tokyo

WATANABE H.
Public Health Institute
of Hyogo Prefecture
2-1 Aratacho, Hyogoku
Kobe City

JUGOSLAVIJA

AČKO M.
Institut za patolosko
morfologijo
Zaloška 4
61 005 Ljubljana

BOGOMIL H.
Dispanzer für Arbeitsmedizin
Zdravstveni dom Celje
Zvezna 8
63000 Celje

BYRNE A.
Institute "Jožef Stefan"
Ljubljana
Jamova 39

ČERKEZ F.
Institute of Hygiene
Medical Faculty
71 000 Sarajevo
Bjelave 70/I

DJUKIĆ Z.
Health Protection Department of the "Boris Kidric"
Institute of Nuclear
Sciences
11 000 Beograd
P.O.B. 522

HOČEVAR B.
Sanitary Inspector
Republiski Sekretariat za
Zdravstvo in Socialno Varstvo
Zupanciceva ul 6 - Pp 644
Ljubljana

KORICANAC Z.
Institute of Inorganic &
Analytical Chemistry
Faculty of Pharmacy
University of Belgrade
Dr. Subotica 8
11 00 Beograd

MILIC S.
Institute of Occupational
& Radiological Health
11 000 Beograd
Deligrdska 29

MILOVANOVIC L.
Institute of Inorganic &
Analytical Chemistry
Faculty of Pharmacy
Dr. Subotica 8
11 000 Beograd

ORUŠEV T.
Institut de Médecine du Travail
Rudnici i Železarnica
Skopje

ROSIVAL L.
Research Institute of Hygiene
Bratislava
Ul.Cs.armady 40

STANKOVIČ B.
Institute of Inorganic and Analytical Chemistry
Faculty of Pharmacy
Studentska 43/10
11 000 Beograd

STANKOVIČ M.
Institute of Occupational and Radiological Health
11 000 Beograd
Deligradska 29

VERHOVNIK V.
62000 Maribor
Kamniska 28

VERHOVNIK Vilma
62000 Maribor
Kamniska 28

WEBER O.
Institute for Medical Research
Yugoslav Academy of Sciences and Arts
P.O. Box 293
Mose Pijade 158
41 001 Zagreb

ZARKOVIC G.
Institut za Higijenu i Socijalnu Medicinu
Moše Pijade 6
71 000 Sarajevo

ZELENKO V.
Institut Joseph Stephen
Ljubljana
Okiskega A

ZUNIC R.
Zajednica za naucno istrazivanje zivotnih uslova
23 ul.Cara H. Selasija
11 000 Beograd

LIBERIA

WESLEY J.
Liberian Embassy
8 rue Jacques Bingen
75017 Paris, France

LUXEMBOURG

LANGEVIN M.
177 rue de Dippach
Bertrange

MAROC

AZIZI A.
Ministère de la Santé
Publique
1 boulevard Jeanne d'Arc
Rabat Agdal

CHAUDERON J. J. M.
Ministère du Travail
11 rue des Courlis
Casablanca

MAURITIUS

MAURICE J.
Ministère de la Santé
Ile-Maurice

MEXICO

BRAVO A, H.
Instituto de Geofisica
Universidad Nacional
Autonoma de Mexico
Torre de Ciencias - 50. Piso
Ciudad Universitaria
Mexico 20

LOWE A. C.
Instituto de Geofisica
Universidad Nacional
Autonoma de Mexico
Torre de Ciencias - 50.Piso
Ciudad Universitaria
Mexico 20

NEDERLAND

BIERSTEKER K.
Municipal Health Department
Baan 170
Rotterdam

den BOER M. C.
Ministerie van Volksgezondheid
D.G. Milieuhygiene
Dr. Reyersstraat 10
Leidschendam

BOLIJN A. G.
Bedrijfsgeneeskundige
Dienst
Hoogovens IJmuiden BV
Medisch Centrum 3D.10
IJmuiden

de BRUIN A.
Universiteit van Amsterdam
Laboratorium van Arbeidshygiene
1^{e} Constantijn Huygensstraat 20
Amsterdam

CANTON J. H.
Rijks Instituut voor de
Volksgezondheid
Postbus 1
Bilthoven

del CASTILHO P.
Laing's Nekstraat 49
Amsterdam

EVENDIJK J. E.
Dienst Centraal Milieu-beheer Rijnmond
Stationsplein 2
Schiedam

GOOTJES P.
Rijks Instituut voor de Volksgezondheid
Postbus 1
Bilthoven

GUPTA S.
Department of Toxicology
Rijks Instituut voor de Volksgezondheid
Postbus 1
Bilthoven

HENDERSON P. T.
Farmacologisch Instituut
Geert Grooteplein noord 21
Nijmegen

HERZBERG S.
Koninklijke/Shell-Laboratorium
Badhuisweg 3
Amsterdam-Noord

JOOSTING P. E.
TNO Research Institute for Environmental Hygiene
Schoemakerstraat 97
P.O.B. 214
Delft

KOLK J. J.
AKZO Research and Engineering
Velperweg 76
fabriek Kleefse Waard
Arnhem

van der KREEK F. W.
Ministerie van Volksgezondheid en Milieuhygiene
Dokter Reijersstraat 10
Leidschendam

van der LEE C. G.
AKZO Research and Engineering
Postbus 60
Arnhem

de MOOR A. G.
Ministerie van Volksgezondheid en Milieuhygiene
Veterinaire Hoofdinspectie
1e van den Boschstraat 4
Den Haag

van der NOORDAA J.
Organization for Industrial Research
Industrial Liaison Dept.
97 Schoemakerstraat
Delft

NOTTEN W. R. F.
Farmacologisch Instituut
Geert Grooteplein noord 21
Nijmegen

OOMS A.
Chemisch Laboratorium TNO
Postbus 45
Rijswijk (Z.H.)

SCHNEIDER T.
Rijksinstituut voor de Volksgezondheid
Postbus 1
Bilthoven

SIBINGA MULDER J.
Bedrijfsgeneeskundige Dienst
Hoogovens IJmuiden BV
Medisch Centrum 3D.10
IJmuiden

den TONKELAAR E. M.
Rijksinstituut voor de Volksgezondheid
Postbus 1
Bilthoven

VERBERK M. M.
Universiteit van Amsterdam
Laboratorium van Arbeidshygiene
1e Constantijn Huygensstraat 20
Amsterdam

de VRIES J.
Organization for Industrial Research
Industrial Liaison Dept.
97 Schoemakerstraat
Delft

de ZEEUW
Instituut voor Toepassing
van Atoomenergie in de
Landbouw
Postbus 48
Wageningen

ZIELHUIS R. L.
Universiteit van Amsterdam
Laboratorium van Arbeidshygiene
1e Constantijn Huygensstraat 20
Amsterdam

NIGERIA

SULAIMAN A. B.
Environmental and Occupational Unit
Federal Ministry of Health
Yakubu Gowon Street
Lagos

NORGE

AASETH J.
Institute of Clinical
Biochemistry
University of Oslo
Rikshospitalet
Oslo 1

SKOGVOLD O. F.
Norwegian Institute for
Air Research
P.O. Box 115
2007 Kjeller

THRANE K. E.
Norwegian Institute for
Air Research
P.O. Box 115
2007 Kjeller

WANNAG A.
Institute of Occupational
Health
Box 8149
Oslo-Dep
Oslo 1

ÖSTERREICH

CZEDIK-EYSENBERG P.
Österreichische Unilever
Ges.M.B.H.
Schenkenstrasse 8-10
1010 Wien

HAIDER M.
Institut für Umwelthygiene
der Universität Wien
Kinderspitalgasse 15
1095 Wien

PFANNHAUSER W.
Forschungsinstitut der
Ernährungswirtschaft
Blaasstrasse 29
1190 Wien

PLANK S.
Ludwig Boltzmann-Institut
für Umweltwissenschaften
und Naturschutz
Heinrichstrasse 5
8010 Graz

STOTT N. B.
Environmental and Medical
Sciences Division
A.E.R.E.
Harwell
Didcot
Berkshire

STREHLOW C.
St. Mary's Hospital
Medical School
Paediatric Unit
Norfolk Place
London W.2.

SWANN P. G.
Esso Petroleum Co. Ltd.
Esso House
Victoria Street
London SW1E 5JW

TAYLOR J. F.
Chloride Batteries Ltd.
P.O. Box 5
Clifton Junction
Swinton
Manchester M27 2LR

TWIBELL J. D.
Home Office Central
Research Establishment
Aldermaston
Near Reading
Berkshire

VAILE H.
Commonwealth Smelting Ltd.
St. Andrews Road
Avonmouth
Bristol BS11 9HP

WAKELIN E. N.
Environmental Services
Department
Trafalgar House
Paradise Circus Queensway
Birmingham B1 2BQ

WALLER R. E.
Medical Research Council
Air Pollution Unit
St. Bartholomew's Hospital
Medical College
Charterhouse Square
London EC1M 6BQ

WILLIAMS M. K.
Chloride Automotive
Batteries Ltd.
Fortyfoot Road
Leatherhead
Surrey

WILSON J. R.
British Gas
45 Oaken Lane
Claygate
Esher
Surrey KT10 0RQ

WOOLLEY J. F.
Standard Telephones Ltd.
Harlow
Essex

YEOMAN W. B.
Regional Toxicology
Laboratory
Dudley Road Hospital
P.O. Box 293
Birmingham B18 7QH

UNITED STATES OF AMERICA

ALBERT R.
New York University
Medical Center
Institute of Environmental
Medicine
550 First Avenue
New York, N.Y. 10016

ALLEN C.
Veterans Administration
Veterans Hospital
Madison, Wisconsin

ALLEN J. R.
Department of Pathology
University of Wisconsin
Medical School
470 North Charter Street
Madison, Wisconsin 53706

ANDERSON J.
Department of Biology
Texas A & M University
College Station
Texas 77813

BARTH D. S.
Environmental Protection
Agency
National Environmental
Research Center
Las Vegas, Nevada 89114

BOUHUYS A.
Yale University Lung
Research Center
333 Cedar Street
New Haven
Connecticut 06510

BRAMAN R. S.
University of South Florida
Department of Chemistry
Tampa
Florida 33620

BURGER E. J.
Science and Technology
Policy Office
National Science Foundation
Washington D.C. 20550

BUSH B.
New York State Department
of Health
Division of Laboratories
and Research
New Scotland Avenue
Albany
New York 12201

BUTLER R. C.
E. I. du Pont de Nemours
& Co.
Petroleum Chemicals
Division
Wilmington
Delaware 19898

CALANDRA J. C.
Northwestern University
and Industrial Bio-Test
Laboratories Inc.
1810 Frontage Road
Northbrook
Illinois 60062

CAPURRO P. U.
Elkton
Maryland 21921

CARNOW B. W.
University of Illinois
School of Public Health
P.O. Box 6998
Chicago
Illinois 60680

CHAPMAN R. S.
Environmental Protection
Agency
National Environmental
Research Center
Research Triangle Park
North Carolina 27711

CLAYTON J. W.
Environmental Protection
Agency
Health Effects Division
Room 609 West Tower WSM
401 M Street SW
Washington D.C. 20460

COMMINS J.
J. A. Commins & Associates
7708 Orchard Way
Philadelphia
Pennsylvania 19118

COOPER W. C.
Tabershaw Cooper Associates
2180 Milvia Street
Berkeley
California 94704

CRANMER M. F.
National Center for Toxicological Research
Jefferson
Arkansas

CROCKER K.
Southern California College
2525 Newport Boulevard
Costa Mesa
California 92626

CROCKER T. T.
University of California
Department of Community &
Environmental Medicine
Irvine
California 92664

DAVID O.
State University of New York
Downstate Medical Center
451 Clarkson Avenue
Box 1195
Brooklyn
New York 11203

DAVISON T. H.
Chicago & North Western
Transportation Co.
500 W. Madison Street
Chicago
Illinois 60606

DONALDSON W. T.
Environmental Protection
Agency
Southeast Environmental
Research Laboratory
College Station Road
Athens
Georgia 30601

DUNCAN S.
Institute for Research
in Hypnosis
315 E 77th Street
New York City
New York 10021

EDWARDS H. W.
Colorado State University
Department of Mechanical
Engineering
Foort Collins
Colorado 80521

ENGEL R. E.
Environmental Protection
Agency
Office of Research and
Development
401 M Street SW
Washington D.C. 20460

ENGLISH T.
Environmental Protection
Agency
National Environmental
Research Center
Research Triangle Park
North Carolina 27711

EPSTEIN S. S.
School of Medicine
Department of Pharmacology
Cast Western Reserve
University
Cleveland
Ohio 44106

FISHBEIN L.
National Center for
Toxicological Research
Jefferson
Arkansas 72079

FISHER F.
Office of Toxic Substances
Environmental Protection
Agency
Room E-705-B
401 M Street SW
Washington D.C. 20460

FREEMAN G.
Stanford Research
Institute
333 Ravenswood Avenue
Menlo Park
California 94025

FRIEDMANN J.
University of California
Department of Psychiatry
Irvine
California 92664

GARDNER D. E.
Environmental Protection
Agency
Experimental Biology
Laboratory
National Environmental
Research Center
Research Triangle Park
North Carolina 27711

GOLDBERG A. M.
Johns Hopkins University
615 N. Wolfe Street
Baltimore
Maryland 21205

GOLDSMITH J. R.
National Cancer Institute
and California State
Health Department
7910 Woodmont Avenue
Bethesda
Maryland 20014

GOLDSTEIN I.
Columbia University
Division of Epidemiology
School of Public Health
600 W 168th Street
New York
New York 10032

GREEN F.
Environmental Protection
Agency
Waterside Mall
401 M Street SW
Washington D.C. 20460

GRIFFIN H.
Graduate School of Public
Health
University of Pittsburgh
Pittsburgh
Pennsylvania 15261

GROSSMAN A. M.
Los Angeles County Air
Pollution Control District
8712 Wilshire Boulevard
Beverly Hills
California 90211

GUINEE V. F.
New York City Department
of Health
377 Broadway (4th floor)
New York
New York 10013

HANG Y.
New York State Agricul-
tural Expt. Station
Food Research Laboratory
Geneva
New York 14456

HELLMAN R. A.
U.S. Senate Committee on
Public Works
Minority Counsel
Room 4210/Dirkson
Senate Office Building
Washington D.C.

HINE C. H.
University of California
School of Medicine
60 King Avenue
Piedmont
California 94611

HUETER F. G.
Environmental Protection
Agency
National Environmental
Research Center
Special Studies Staff
Research Triangle Park
North Carolina 27711

JACKSON D.
Environmental Protection
Agency
Office of the Administrator
401 M Street SW
Washington D.C. 20460

KAMINSKI E. J.
Northwestern University
Medical School
303 East Chicago Avenue
Chicago
Illinois 60611

KARLAN M. S.
Beverly Hills Medical
Society
Environmental Pollution
Control
9730 Wilshire Boulevard
Beverly Hills
California

KEITZ E. L.
The Mitre Corporation
1820 Dolley Madison Bvd
McLean
Virginia 22101

KENNEDY G. L.
Industrial Bio-Test
Laboratories Inc.
1810 Frontage Road
Northbrook
Illinois 60062

KLEMPERER E.
Institute for Research
in Hypnosis
315 East 77th Street
New York
New York 10021

KNEIP T.
Institute of Environmental Medicine
New York University Medical Center
550 First Avenue
New York
New York 10016

KNELSON J. H.
Environmental Protection Agency
University of North Carolina
Mason Farm Road
Chapel Hill
North Carolina 27514

LAUER G.
Rockwell International
Science Center
1049 Camino Dos Rios
Thousand Oaks
California 91360

LEUNG S.
California Air Resources Board
638 Coolidge Street
Davis
California 95616

LEVERE T. E.
North Carolina State University
Department of Psychology
Raleigh
North Carolina 27607

LIU B. Y. H.
University of Minnesota
Mechanical Engineering Department
Minneapolis
Minnesota 55455

LLOYD W. J.
National Institute for Occupational Safety and Health
5600 Fishers Lane
Room 10-28
Rockville
Maryland 20852

LYNAM D. R.
International Lead Zinc
Research Organization Inc.
292 Madison Avenue
New York
New York 10017

McCABE E. B.
International Lead Zinc
Research Organization Inc.
1202 Frisch Road
Madison
Wisconsin 53711

McCARTY D. L.
3810 East Coast Highway
Suite One, Corona del Mar
California 92625

McNEIL J.
Texas Technical University
School of Medicine
Suite H, 6211 Edgemere
El Paso
Texas 79925

McNESBY J. R.
National Bureau of Standards
Washington D.C. 20234

METZGER R.
Department of Physical Science
San Diego State University
San Diego
California 92115

METZGER S.
Department of Physical Science
San Diego State University
San Diego
California 92115

MICHAELSON I. A.
University of Cincinnati
College of Medicine
Department of Environmental Health
3223 Eden Avenue
Cincinnati
Ohio 45219

MITCHELL R. I.
Battelle Columbus Laboratories
505 King Avenue
Columbus
Ohio 43201

MORRIS S.
Brookhaven National Laboratory
Upton
New York 11973

MRAK E. M.
Environmental Protection Agency
University of California
Davis
California

MUIR W.
Executive Office of the President
Council on Environmental Quality
722 Jackson Place NW
Washington D.C. 20006

NEEDLEMAN H.L.
Children's Hospital Medical Center
300 Longwood Avenue
Boston
Massachusetts 02115

NELSON N.
New York University
37 Detries Avenue
North Tarry Town
New York 10591

O'KEEFFE A. E.
Environmental Protection Agency
Chemistry and Physics Laboratory
National Environmental Research Center
Research Triangle Park
North Carolina 27711

OMENN G.
Office of the Chairman
B-413
Atomic Energy Commission
Washington D.C. 20545

OREL J. V.
Environmental Consultant
522 Warner Avenue
Los Angeles
California 90024

PALLOTTA A. J.
Environmental Protection Agency
401 M Street SW
East Tower Room 401
Washington D.C. 20460

PETERSON R. W.
Chairman of the President's Council on Environmental Quality
722 Jackson Place NW
Washington D.C. 20460

RALL D.
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park
North Carolina 27709

REEF A.
AMAX Inc.
1270 Avenue of the Americas
New York
New York 10020

REEVES A.
Wayne State University
School of Medicine
540 East Canfield
Detroit
Michigan 48201

REUTER L.
Sanitary Engineer
Research Branch
U.S. Army Medical R & D Command
Washington D.C. 20314

RUBIN R. J.
Johns Hopkins University
School of Hygiene and Public Health
615 N Wolfe Street
Baltimore
Maryland 21205

SANTOLUCITO J. A.
Environmental Protection Agency
Pesticide and Toxic Substances Effects Lab.
National Environmental Research Center
Research Triangle Park
North Carolina 27711

SCHUCK E. A.
Environmental Protection Agency
National Environmental Research Center
P.O. Box 15027
Las Vegas
Nevada 89114

SCHWING R. C.
General Motors Corporation
Technical Center
Warren
Michigan 48090

SILBERGELD E. K.
Johns Hopkins University
615 N Wolfe Street
Baltimore
Maryland 21205

STARA J. F.
Environmental Protection Agency
Office of Research and Development
National Environmental Research Center
Cincinnati
Ohio 45268

STEELE T. D.
Department of Interior
Geological Survey - Water Resources Division
Quality of Water Branch
Washington D.C.

SUTHERLAND L. C.
Wyle Laboratories
128 Maryland Street
El Segundo
California 90245

TER HAAR G.
Ethyl Corporation
Research and Development Department
1600 West Eight Mile Road
Ferndale
Michigan 48220

TRAKOWSKI A. C.
Environmental Protection Agency
Waterside Mall
401 M Street SW
Washington D.C. 20460

WALSH R. G.
Office of Research and Development
Environmental Protection Agency
Washington D.C. 20460

WARNER P. O.
Wayne County Department of Health
Air Pollution Control Division
1311 East Jefferson
Detroit
Michigan 48207

WEAVER N. K.
American Petroleum Institute
1801 K Street NW
Washington D.C. 20006

WEIR F. W.
Biomedical Science Dept.
Research Laboratories
General Motors Corporation
Technical Center
Warren
Michigan 48090

WEISS B.
University of Rochester
School of Medicine and Dentristry
Department of Radiation Biology and Biophysics
Rochester
New York 14642

WESOLOWSKI J. J.
Air and Industrial Hygiene Laboratory
California State Department of Health
2151 Berkeley Way
Berkeley
California 94704

WETHERILL G. W.
Department of Planetary and Space Science
University of California
Los Angeles
California 90024

WIERZBICKI R.
3745 West 56th Street
Chicago
Illinois 60629

YANIV S. L.
Environmental Protection Agency (HM-571)
Washington D.C. 20460

YU M.-H.
Huxley College of Environmental Studies
Wast Washington State College
Bellingham
Washington 98225

ZAVON M. R.
Ethyl Corporation
451 Florida Avenue
Baton Rouge
Louisiana 70801

ZBAR J. E.
Bellevue Hospital
New York City
2690 Kennedy Boulevard
Jersey City
New Jersey 07306

U.S.S.R.

SANOTSKY A.
Institute of Industrial Hygiene and Occupational Diseases
Academy of Medical Sciences
31 Meyerovskij Prozd
Moscow E 273

VENEZUELA

SALAS-BERTI M.
Dirección de Malariología y Saneamineto Ambiental
Ministerio de Sanadad y Asist. Social
Apartado 2676
Caracas 101

ADMINISTRATIVE STAFF

Conference Officers:	D. BLAND (EPA) A. BONINI (CEC) E. MILLAR (CEC) R. MILLAR (CEC) T. SONNEN (CEC)
Press Officers:	G. ANOUIL (CEC) J. PARRISH (EPA) R. REPOND (WHO)
Editorial Board:	W. BRAY (CEC) B. O'NEILL (CEC)
Technical Services:	R. LINSTER (CEC)
Secretariat:	S. BRAMAN (WHO) A. DOYLE (EPA) M. PASSERINI (EPA) L. PROOST (CEC)

2522.a.

VERZEICHNIS

INDEX

INDEX

INDICE

INDEX

AASETH, J., 913
ADLER, M.W., 77
ALBERT, R., 1167, 2061, 2068, 2069
ALESSIO, L., 1123, 1129, 1130, 1167
ALLART-DEMUL, C., 1303
ALLEGRINI, M., 1697
ALLEN, J.R., 385, 397
ALTMAN, D.G., 289
ALTSHULER, B., 2061
ALTSHULLER, A.P., 2109
ANDERSON, J., 1449, 1461, 1468, 1469
ANGERER, J., 1317, 1327, 1328
ARHIRII, M., 339
ARONOW, R., 1177
ARSAC, F., 603
AUBERT, M., 1613

BABCOCK, L.R., 2083
BACKHAUS, F., 2231
BAKER, F.D., 879
BARHAD, B., 333
BARQUET, A., 695
BARRATT, R.S., 1397, 1779
BARSAN, E.T., 1073
BARTH, D.S., 1875, 1877, 1921, 1922, 1925, 1926, 1928, 1930, 1931, 1933, 1934, 1935, 1939, 1940, 1950, 1959, 1960, 1962, 1963, 2073,
BASTENIER, H., 1303
BATES, D.V., 1007, 1967, 1978, 1979, 2001, 2003, 2162
BATTI, R., 1531
BEACONSFIELD, P., 2397
BECK, E.G., 1031, 1040, 1041
BEITZ, L., 1417, 1430
BELCHER, R., 1779
BELL, A., 1101
BENARIO, M., 2169
BENINSON, D., 845, 1878, 1924, 1927, 1934, 1935, 1941, 1949, 2297
BENSON, F.B., 423
BERGLUND, B., 119
BERGLUND, U., 119, 142
BERLIN, A., 552, 611, 629, 693, 859, 1087, 1100, 1238, 1959, 2003, 2185, 2254, 2257
BERLIN, M., 156, 491, 895, 1259
BERNA, M., 231
BERNER, A., 1729
BERNSTEIN, A.D., 105, 116, 117, 1029, 2298
BERNSTEIN, D., 431
BIANCO, A., 1039
BIERSTEKER, K., 1881, 1924, 1926, 1933, 1934, 1943, 1957, 1958, 1959
BIGNON, J., 1189, 1196, 1197
BINDER, R.E., 669
BITTEL, R., 714, 1441, 1449, 1469
BLACKBURN, C.R.B., 63
De BOECK, R., 1131
Den BOER, M.C., 1247
BOGDANOVIC, E., 2271
BONNAUD, G., 1189
BONNEFOUS, M., 510

Underlined numerals denote authors
Arabic numerals denote participants in discussions

BORDAS, E., 1145
del BORGHI, M., 1807
BORLAUG, N., 2397
de BORTOLI, M., 1287
BOTZENHART, K., 1757
BOUDENE, C., 603, 612
le BOUFFANT, L., 1645, 1651
BOUHUYS, A., 669, 675
BOUQUIAUX, J., 1239, 1298
BOURBON, P., 269
BOURDEAU, Ph., 263 363, 366, 510
BOUVILLE, A., 1531
BRADEN, M., 485
BRAETTER, P., 2255, 2301
BRAMAN, R.S., 117, 258, 1328, 1363, 1370, 1397, 1954
BRAVO A, H., 468, 2091, 2160, 2161
BREIDENBACH, A.W., 751
BRILLE, D., 269, 356, 667
BROCKHAUS, A., 781
BROMBERG, P.A., 1989
BROOKS, A.G.F., 77
BRUAUX, P., 1131, 1143
BRUCH, J., 781, 791, 1040, 1206
de BRUIN, A., 259, 911, 2059
BUCHET, J.P., 631, 887, 2185
BULCRAIG, W.R., 209
BURGER, E.J.jr., 145, 155, 156, 157
BUSH, B., 879, 885, 911, 1339
BUSTUEVA, K., 1009
BUTLER, G.C., 1431, 1884, 1930 1937, 1948, 1955, 1956, 1978
BUXTON, R. St.J., 1113
BYRNE, A.R., 245, 258, 259, 260, 1370
CACCURI, S., 1823
CAGNETTI, P., 1451
CALANDRA, J.C., 772
CANTON, J.H., 1479, 1489
CAPURRO, P.U., 1579
CARNOW, B.W., 45, 313, 353, 266, 368, 588, 1129, 1167
CARPENTER, L., 1729
CARPI di RISMINI, A., 2397
CARSTENS, L.A., 385
CARSTENSEN, J., 969
CARTER, M.H., 1399
del CASTILHO, P., 2185
CASULA, D., 1693
CERNIK, A.A., 1207, 1221, 1237, 2254
CERQUIGLINI-MONTERIOLO, S., 1301 1383
CHAMBERS, P., 104, 259, 397, 510, 702, 2045
CHANTEUR, J., 2386
CHAPMAN, R., 193, 207, 208, 210, 645, 658
CHARLTON, J., 1120
CHATTOPADHYAY, A., 1685
CIALELLA, N., 2225
CICOLELLA, A., 1661
CIGNA ROSSI, L., 1451
CLAEYS-THOREAU, F., 1131
CLAUDE, J.R., 397
CLAYTON, J.W.jr., 371, 383, 383
CLEMENTE, G.F., 260, 1028, 1451, 2298
COFFIELD, T.H., 858
COIN, L., 703
COLMAN, R., 485
COLOMBINI, M., 159

COLUCCI, A.V., 1043
COOPER, W.C., 555, 568, 569, 1196
COTE, R.W., 47
CROCKER, K., 2068
CRÖSSMANN, G., 1407
CRUZ, R., 1685
CUCU, M., 333

DAHL, R., 2231
DAMS, E., 513, 1430
DAMS, R., 409
DANIEL, H., 1645, 1651
DANIEL, J.W., 877, 902, 1041
DANIELSON, L., 116, 885
DAVID, O., 588, 1549
DAVIDOW, B., 545
DAVIES, J.E., 695
DAVOUST, P., 2384
DEAN, G., 190, 643
DEHNEN, W., 781
DELEANU,M., 1583
DELCARTE, E., 1675
DELVES, H.T., 2215, 2258
DEMUYNCK, M., 409
DENNIS, C.A.R., 1029, 1543, 1953
DEPAUS, R., 1341
von DEPKA, J., 506
DERWENT, R.G., 1669
DESBORDES, J., 1199
DEVOTO, G., 1693
DIEHL, J.F., 958, 1121
DIETERICH, B.H., 2451
DIETL, F., 1853
DI FERRANTE, E., 1956
DJURIC, D., 1829
DOBIN, D.D., 1223
DOBRYSZYCKA, W., 685
DOLGNER, R., 279
DONALDSON, W.T., 1399, 1405, 1406
DONNIER, B., 1613
DONZELLI, A., 231
DUBOIS, L., 1331
DUGANDZIC, M. 2285
DUMONT, M., 2231
DUNCAN, K.P., 2175
DUNCAN, L.J., 1241
DUPUIS, P.J., 491, 1196, 1314

EDWARDS. H.W., 1277, 1285, 1286
EFTHYMIOU, M.L., 1789
EGELS, W., 1407
EISENBUD, M., 431
ENGLISH, T.D., 401, 470, 471, 472
EPSTEIN, S.S., 552, 569, 749, 814, 1120, 2367, 2382, 2383, 2384, 2385, 2386
van ESCH, G.J., 1017
ESPINOSA, M.E., 2091
EVENDIJK, J.E., 1351

FACCHETTI, S., 1287, 1298, 1299
FAGNIART, E., 1675
FAIRWEATHER, F.A., 1113
FALK, H.L., 2331, 2348, 2349, 2350
FAVRETTO, L., 1511
FAVRETTO GABRIELLI, L., 1511
FERRAIOLO, E.G., 1807

FERRARI-BRAVO, F., 1797
FINE, P.R., 1223
FINKLEA, J., 193, 645
FISCHER, A.B., 1031
FISHBEIN, L., 725, 749
FLOREY, C., 289
FONDIMARE, A., 1199, 1206
FOURNIER, E., 1433, 1439, 1789
FREDERIKSON, M., 1959
FREEMAN, G., 685, 833, 844, 1007
FRENCH, J., 193, 645
FRIBERG, L., 2307, 2315, 2316
FRIEDMANN, J., 507, 510, 511
FRIEDRICHS, K.H., 715, 723, 724
FUMAROLA, G., 1807
FURIOSI, N.J., 833

GADDO, P.P., 1287
GAFFEY, W.R., 555
GAGE, J.C., 895
GAGLIONE, P., 1287
GARDI, R., 1807
GARDNER, D.E., 705, 713, 714,
GARIBALDI, P., 1287
GARNIER, A., 1441
GENT, M., 1263
GHELBERG, N.W., 1145, 1583
GHETTI, P.F., 1957
GIANANI, G., 1697
GIBBS, G.W., 1197, 1206, 2271, 2296, 2297, 2301, 2302
GIBSON, R.J.W., 289
von GIERKE, H., 1249
GIOVANNINI, I., 1797
GLAUDE, P., 1341
GLOBUS, G., 507
GODIN, J., 603
GOERKE, W., 37
GOLDBERG, A.M., 793, 803
GOLDBERG, H., 193
GOLDSMITH, J.R., 62, 155, 189, 382, 585, 675, 1889, 1923, 1935, 1936, 1942, 1945, 1950, 1956, 2156, 2165, 2179,
GOLDSTEIN, I., 1275
GONO, E., 591
GOOTJIS, P., 1316, 1951
GRAB, B., 339
GRADISKI, D., 1631, 1661
de GRAEVE, J., 523
GRAOVAC-LEPOSAVIC, L., 1829
GRASSO, C., 861, 878
GREENLAND, R.D., 805
GREVE, P.A., 1479
GRIECO, A., 231
GRIFFIN, H.E., 2305
GROLL-KNAPP, E., 989
GROS, R., 2225
GRUENER, N., 1067
GRÜNSPAN, M.J., 773, 2003
GUINEE, V.F., 545, 551, 552, 553, 1166

HAAG, A., 1317
HAASE, J., 1417
HADDAD, R., 451
HAGEDORN-GOETZ, H., 2231
HAIDER, M., 475, 989, 999, 2393
HARDWICK, D.F., 961
HARKE, H.P., 1327, 1773
HARRISON, P.R., 1741
HARRISON, R.M., 1111, 1285, 1349, 1370, 1405, 1783

HAYES, C., 645
HAZUCHA, M., 1979, 2001
HEBBELINCK, D., 1303
HEM, B., 1189
HENDERSON, P.Th., 2047
HENIN, J.P., 1651
HERNBERG, S., 568, 692, 1129, 1142, 2395
HERTZ, M.B., 1763
HICKEY, N., 658
HILLERY, P.J., 7
HILPERT, K., 2231
HINE, C.H., 207, 260, 1040, 1130, 1937, 2029, 2298
HINTON, D.O., 1769
HISLOP, J., 959
HO, M.T., 1519
HOFMAN, B., 1017
HÖGGER, D., 1247, 2157
HOLL, K., 612
HOLLAND, W.W., 39, 45
HOLM, S., 895, 902
HOLMQVIST, I, 613, 629
HORIE, Y., 2143
HOSEIN, H.R., 669
HOUCK, C.L., 879
HOWER, J., 591, 601
HUETER, F.G., 261, 352, 363, 364
HUTCHINSON, T.C., 1685
HUTH, F., 715
HUUNAN-SEPPÄLÄ, A., 2263

IMPENS, R., 1675
IOVENITTI, L., 1797
IRWIG, L., 289, 360
IWANKIEWICZ, S., 685
IZMEROV, N.F., 2409
JACKSON, D.L., 161, 176, 177, 178, 1956
JACOBSEN, M., 89, 211, 228, 229, 1478, 1502, 2365
JACYSZYN, K., 685
JAMIN, P., 523
JANSEN, G., 513, 999, 2044
JEANMAIRE, L., 2225, 2252, 2256
JERVIS, R.E., 1685
JOHNSON, D.L., 1363
JOOSTING, P.E., 76, 2005, 2029
JOST, D., 2115
JUHOS, L., 833

KAMINSKI, E.J., 551, 803, 1168
KARCHER, W., 1341, 1349
KARHAUSEN, L., 367
O'KEEFFE, A.E., 2109, 2164, 2166 2168, 2169, 2172
KEITZ, E.L., 1241, 1247, 1248
KELLER, M.D., 47
KEVANY, J., 89
KILPIÖ, J.O., 2263
KIRCHMANN, R., 1675
KJELLSTRÖM, T., 62, 1221, 1939, 2197, 2252, 2254, 2257, 2299, 2303, 2328, 2365, 2383
KLAHRE, P., 2231
KLEINMAN, M., 431
KNAUTH, P., 2031, 2043, 2044
KNEIP, T.J., 431, 466, 473
KNELSON, J.H., 181, 189, 190, 361, 973
KOPPLE, J.D., 847
KORICANAC, Z., 2285
KOSTA, L., 245
KOTLAREK-HAUS, S., 685, 692, 693

KRACKE, W., 1853
KREBS, H., 2397
van der KREEK, F.W., 959, 1028, 1065, 2382
KREUZER, W., 601, 1853, 2045, 2299
KUMMER, J., 1303, 1314, 1315, 1316, 1339
KUMPF M.J., 339, 363, 365, 1957

LACOURLY, G., 1441
LAFONTAINE, A., 382, 1131, 1942, 2437
LAMBO, T.A., 11
LANESE, R.R., 47
LANG, R., 659
LANGER, H., 1757
LANZOLA, E., 1697
LAO, R.C., 1331, 1339, 1340, 1468
LAUER, G., 423, 2156, 2163
LAUWERYS, R., 542, 568, 631, 831, 887, 1238, 2185
LEEDER, S.R., 63, 76, 1111
LEFEVRE, M.J., 988, 2029
LEGRAND, M., 1131
LEHNERT, G., 1317
LEHTO, V.P., 1007, 2315
LELLOUCH, J., 269
LENGHEL, I., 1583
LEUNG, S., 1248
LEVERE, T.E., 493, 506
LEVY, D., 1263, 1275, 1276
LEVY, E.A., 1797
LIND, B., 2197
LINDVALL, T., 119, 1954
LINNMAN, L., 2197
LLOYD, W.J., 1085
LO, Fa-Chun, 879
van LOON, J., 1685, 1849
LORKE, D., 817, 830, 831
LÖSER, E., 817
LOVE, G.J., 301, 645
LOWE, A.C., 2091
LYNAM, D.R., 543, 791

MAGADUR, J.L., 1631, 1661
MAGE, D., 176, 207, 1275, 2068, 2156, 2158, 2162, 2164, 2165, 2168, 2170, 2174, 2176, 2178, 2179, 2181, 2315, 2364
MAGE, D.T., 2097
MAGI, F., 857
MAGNAVAL, R., 1531
MAHEU, R., 17
MALONE, D.W., 1569
MANOJLOVIC, N., 1031
MARCUS, A.H., 1505
MARQUARDT, H., 1607
MARTIN, A.E., 1113, 1120, 1121, 1122, 2305
MARTIN, J., 973
MARTIN, J.C., 1645, 1651
MATERNE, D., 631
McCABE, E.B., 1168
McDONALD, G.C., 1491
McGUIRE, J.M., 1399
McNEIL, J.L., 571, 584, 586, 588, 589
McNESBY, J.R., 1371, 1383
MEININGER, J., 603
van MEIRHAEGE, A., 2044
MENENTI, M., 1797
MERIAN, E., 929, 1396, 2175

DEMUYNCK M. R. R.
Instituut voor Nucleaire
Wetenschappen
Rijksuniversiteit Gent
Proeftuinstraat 86
9000 Gent

DRUMAUX P.
Ministère Santé Publique
Administration Hygiène
Service des Nuisances
Cité Administrative de l'Etat
1010 Bruxelles

DUHAMEAU W.
Institut National des Industries Extractives
rue de Chéra 200
4000 Liège

FAGNIART E. A.
Département Radiobiologie
CEN/SCK
2400 Mol

GRANDJEAN J. F. F.
Institut Royal Météorologique
de Belgique
Avenue Circulaire 3
1180 Bruxelles

HAWKES A.
Ethyl S.A.
1 rue Paul Lauters
1050 Bruxelles

HERMAN P.
Institut de Recherches Chimiques
Ministère de l'Agriculture
5 Moslenstraat
1980 Tervuren

IMPENS R.
Faculté Sciences Agronomiques
de l'Etat
5800 Gembloux

KUMMER J.
Université Libre de Bruxelles
100 rue Belliard
1040 Bruxelles

KUSTERS E. M. V.
Medische Dienst
BASF Antwerpen NV
Eikenlei 15
2130 Brasschaat

LAFONTAINE A.
Institut d'Hygiène et
d'Epidémiologie
14 rue Juliette Wytsman
1050 Bruxelles

LAUWERYS R.
Unité de Toxicologie Industrielle et Médicale
Université Catholique de
Louvain
Avenue Chappelle aux Champs 4
1200 Bruxelles

LEFEVRE M. J.
Solvay et Co. - DCP
33 rue Prince Albert
1050 Bruxelles

LEGRAND M.
Institut d'Hygiène et
d'Epidémiologie
14 rue Juliette Wytsman
1050 Bruxelles

MERCIER M.
Université de Louvain
Sentier du Biereau 13
1348 Louvain-la-Neuve

NEURAY M.
Institut National des Industries Extractives
rue de Chéra 200
4000 Liège

OVERSTEYNS M.
Metallurgië Hoboken Overpelt
Fabrieksstraat 144
3583 Overpelt

ROELS H. A. C.
Unité de Toxicologie Industrielle et Médicale
Université Catholique de
Louvain
4 Avenue Chapelle aux Champs
1200 Bruxelles

RONDIA D. J. J.
Laboratoire de Toxicologie
Boulevard de la Constitution
4000 Liège

SPAAS J.
Comité de Liaison des Industries de Métaux non Ferreux
de la Communauté Européenne
boulevard de Berlaimont 12
1000 Bruxelles

STASSEN J.-J.
Université de Liège
rue des Augustins 49
4000 Liège

SWYNGEDOUW Y.
Institut d'Hygiène et
d'Epidémiologie
14 rue Juliette Wytsman
1050 Bruxelles

TITE M.
Dépt. de Toxicologie
R.U.G. Belgique
Hospitaalstraat 13
9000 Gent

VAN MEIRHAEGHE A.
Dienst Openbare Gezondheid
Stad Gent
23 Stationstraat
9000 Gent

VUYLSTEEK K.
Institut d'Hygiène et de
Médecine Sociale
Institut d'Hygiene R.U.G.
Akad. Ziekenhuis
De Pintelaan 135
9000 Gent

BUNDESREPUBLIK DEUTSCHLAND

ANGERER J.
Zentralinstitut für
Arbeitsmedizin
2 Hamburg 76
Postfach 56 45

ARSOVIC H. M.
Emissions Technisches
Institut
757 Baden-Baden
Beutigweg 1

BECK E. G.
Hygiene-Institut
Justus-Liebig Universität
63 Giessen
Friedrichstr. 16

BEHNE D.
Hahn-Meitner-Institut für
Kernforschung Berlin GmbH
Bereich Kernchemie und
Reaktor
1 Berlin 39
Glienicker Strasse 100

BEITZ L.
Siemens A.G.
Bereich Mess- und Prozesstechnik
75 Karlsruhe
Rheinbrückenstr. 50

BERGE H.
Institut für Umweltschutz
u. Agrikulturchemie
5628 Heiligenhaus
Bez. Düsseldorf
Am Vogelsang

BRAETTER P.
Hahn-Meitner Institut für
Kernforschung Berlin GmbH
1000 Berlin 39
Glienicker Strasse 100

BRETSCHNEIDER W.
Deutsche Forschungsgemeinschaft
53 Bonn-Bad Godesberg 1
Kennedyallee 40

BRUCH J.
Med. Institut für Lufthygiene
und Silikoseforschung an
der Universität Düsseldorf
4000 Düsseldorf
Gurlittstr. 53

DEIMEL M.
Institut für Lebensmittel-,
Wasser- u. Luftuntersuchungen
der Stadt Köln
5 Köln 1
Eifelwall 7

von DEPKA J.
Rheinische Olefinwerke GmbH
5047 Wesseling
Postfach 31

DIEHL J. F.
Institut für Strahlentechnologie der Bundesforschungsanstalt für Lebensmittelfirschhaltung
75 Karlsruhe 1
Engesserstr. 20

ELLISSEN W.
Chemie-Mineralien K.G.
28 Bremen
Postfach 1804

FISCHER A. B.
Med. Institut für Lufthygiene und Silikoseforschung an der Universität Düsseldorf
4000 Düsseldorf
Gurlittstr. 53

FOERSTER H. J.
Daimler-Benz A.G. Abt.E 6
7000 Stuttgart-Untertürkheim
Postfach 202

FRIEDRICHS K.-H.
Med. Institut für Lufthygiene und Silikoseforschung an der Universität Düsseldorf
4000 Düsseldorf
Gurlittstr. 53

GOERKE W.
Bundesministerium des Innern
53 Bonn
Rheindorferstr. 198

GRAUL E. H.
MEDICEF
355 Marburg/Lahn
Körnerstr. 19

GREFEN K.
Verein Deutscher Ingenieure
Kommission Reinhaltung der Luft
4000 Düsseldorf
Graf-Recke-Str. 84

GROMZIG H.
Stadtverwaltung Duisburg
Gesundheitsamt
41 Duisburg 1
Landfermannstr. 1

GRÜNSPAN M.
Med. Institut für Lufthygiene und Silikoseforschung an der Universität Düsseldorf
4000 Düsseldorf
Gurlittstr. 53

GÜLLEMANN D.
Universität Bielefeld
48 Bielefeld
Postfach 8640

HALBRITTER G.
Institut für Angewandtle Systemtechnik und Reaktorphysik
Kernforschungszentrum
75 Karlsruhe
Postfach 3640

HARKE H.-P.
Forschungsinstitut der Cigaretteninduslire e.V.
Gazellenkamp 38
2 Hamburg 54

HOLL K.
Bundesministerium für Jugend, Familie und Gesundheit
53 Bonn-Bad Godesberg 1
Deutschherrenstr. 87

HOWER J.
Universitätskinderklinik
43 Essen
Hufelandstr. 55

JANSEN G.
Universitätsklinikum
43 Essen
Hufelandstr. 55

KNAUP M.
Arbeitskollektiv Zwei
35 Kassel
Kirchweg 77

KNAUTH P.
Institut für Arbeits-
physiologie an der
Universität Dortmund
Ardeystr. 67
Dortmund

KOPETZ K.
Chemische Werke Hüls A.G.
437 Marl Kreis Recklinghausen
Postfach 1180

KREUZER W.
Bereich für Hygiene und
Technologie der Lebens-
mittel Tierischen Ursprungs
Universität München
8 München 22
Veterinärstr. 13

LANDHÄUSSER O.
Rheinische Ölefinwerke GmbH
5047 Wesseling
Postfach 31

LEHMANN K.
Deutscher Normenausschuss
1 Berlin 30
4-7 Burggrafenstrasse

LORKE D.
Institut für Toxikologie
der Bayer A.G.
56 Wuppertal 1
Fried. Ebertstr. 217

LÖSER E.
Institut für Toxikologie
der Bayer A.G.
56 Wuppertal 1
Fried. Ebertstr. 217

MAINTZ E.
Hamburgische Electricitäts-
Werke A.G.
2000 Hamburg 60
Überseering 12

MATHEIS U.
Institut für Angewandte
Systemtechnik und
Reaktorphysik
Kernforschungszentrum
75 Karlsruhe
Postfach 3640

MENKE J.
Stadtverweltung Mülheim
433 Mülheim-Ruhr
Amt 53, Ruhrstrasse

OLTERSDORF U.
Institut für Ernährungs-
wissenschaft
6300 Geissen
Wilhelmstr. 20

PIETRZOK W.
Arbeitskollektiv Zwei
35 Kassel
Kirchweg 77

POETZL K.
Institut für Atmosphärische
Umweltforschung
8 München 90
Harthauserstr. 109

PRENZEL J.
Staatliches Gesundheitsamt
für den Landkreis Wesermarsch
2880 Brake/Utw.
Rönnelstr. 10

PREUSSMANN R.
Deutsches Krebsforschungs-
zentrum
Institut für Toxikologie
und Chemotherapie
69 Heidelberg
Kirschnerstr. 6

PRINZ B.
Landesanstalt für Immissions-
und Bodennutzungsschutz des
Landes NW
43 Essen - Bredeney
Wallneyer-Str. 6

RAEDE D.
Bayer A.G.
4150 Krefeld
Rheinuferstr. 7-9

RAHLENBECK U.
Fachdokumentation Reinhaltung
der Luft, VDI
4 Düsseldorf 1
Graf-Recke-Str. 84

LEIDNER J.
CES Ecologie Humaine
UER Biomédicale
2 rue Saint Exupéry
92700 Colombes

LEJEUNE X.
Ciba-Geigy S.A.
92505 Rueil Malmaison

LE MOAN R.
Université René Descartes
170 boulevard Ney
75018 Paris

LEYNAUD G.
Division Qualité des Eaux
Pêche et Pisciculture
C.T.G.R.E.F.
14 avenue de St. Mandé
75012 Paris

LIEVAIN O.
Service de Chirurgie
Clinique du Parc Monceau
21 rue de Chazelles
75017 Paris

LOWY R.
C.N.R.S.
Laboratoire de Nutrition
Humaine
Hôpital Bichat
75018 Paris

LUQUET F. M.
Laboratoire d'Industrie
Laitière - E.N.S.I.A.
13 rue de l'Université
59000 Douai

MACLOUF C.
Préfecture de Police
14 rue Brémontier
75017 Paris

MAGADUR J. L.
I.N.R.S.
route de Neufchâteau
54500 Vandoeuvre

MARIEN J.
Laboratoire d'Hygiène
1 bis rue des Hospitalières
St. Gervais
75004 Paris

MEININGER J.
1 boulevard de Vaugirard
75751 Paris Cedex 15

MESNIL M.
Roussel U.C.I.A.F.
102 route de Noisy
Romainville

MICHON G.
C.E.A. Saclay (C.I.R.E.A.)
Boîte Postale 8
91190 Gif sur Yvette

MOLLARET P.
Institut de Médecine et
d'Epidémiologie Africaine
Hôpital Claude Bernard
10 avenue Porte d'Aubervilliers
75019 Paris

MONCEAUX R. H.
Revues Médicales
51 rue de la Procession
75015 Paris

MONCELON B.
I.N.R.S.
route de Neufchâteau
54500 Vandoeuvre

MOREAU M.
Université de Bretagne
Occidentale
Faculté des Sciences
6 av. Victor Le Gorgeu
29283 Brest Cedex

MORICHAU-BEAUCHANT J.
Institut d'Etude du
Développement Economique
et Sociale
5 rue des Colonnes-du-Trône
75012 Paris

MOUTET J.-P.
I.N.S.E.R.M.
44 chemin de Ronde
78000 le Vésinet

MOUVIER G. J.
Université de Paris 7
Laboratoire de Physico-
Chimie Instrumentale
2 place Jussieu
75221 Paris Cedex 05

MOYEN E.
Ministère de la Qualité
de la Vie
14 bd du Général Leclerc
99000 Neuilly/Seine

MUEL B.
Fondation Curie
Institut du Radium
26 rue d'Ulm
75005 Paris

NIEF G.
Commissariat à l'Energie
Atomique
Centre d'Energie Nucléaire
de Saclay
Boîte Postale 2
Jif-sur-Yvette

OPPENEAU J. C.
Ministère de la Qualité
de la Vie
14 bd du Général Leclerc
92000 Neuilly/Seine

ORIOL P.
I.N.S.E.R.M., U. 68
Hôpital Saint Antoine
75571 Paris Cedex 12

OSTROWSKI Z.-L.
C.I.E.
3 Square du Rhône
75017 Paris

PARENTEAU J.P.
Ministère de l'Environnement
13 rue de Bourgogne
75007 Paris

PARROTT J.
De Pietro Press
55 boulevard de Charonne
75011 Paris

PATTI F.
Commissariat à l'Energie
Atomique
Boîte Postale 6
92260 Fontenay-aux-Roses

PERDRIZET S.
I.N.S.E.R.M.
38 rue de Bretagne
75003 Paris

PEYRONNET J.
Laboratoire Central de la
Préfecture de Police
39 bis rue de Dantzig
75015 Paris

PHAM Q. T.
I.N.S.E.R.M., U. 14
Plateau de Brabois
54500 Vandoeuvre lès Nancy

PIVA C,
Hôpital Fernand Widal
200 rue du Fbg St. Denis
75474 Paris-Cedex 10

POUSSE G.
Laboratoire Central de la
Préfecture de Police
39 bis rue de Dantzig
75015 Paris

QUINOT E.
I.N.R.S.
route de Neufchâteau
54500 Vandoeuvre

RAVIART M.
I.M.A.-I.N.S.E.R.M.
Hôpital de Bicêtre
94270 Le Kremlin-Bicêtre

REY COQUAIS B.
Société Prodelec
25 quai Paul Doumer
92408 Courbevoie

RIBARD P.
Centre Antipoison de Lyon
Hôpital Edouart Heriot
69000 Lyon

RIPS R.
I.N.S.E.R.M.
17 rue du Fer à Moulin
75005 Paris

ROBERT E.
Compagnie Française BASF
Département Agricole
140 rue Jules Guesde
Boîte Postale 118
92303 Levallois-Perret

ROTHSTEIN G.
13 rue de Poissy
75005 Paris

ROTHSTEIN M.
13 rue de Poissy
75005 Paris

ROUCH Y.
Médecine du travail et
Hygiène industrielle
Hôtel Dieu
31052 Toulouse

ROUIT C.
Société Française des
Pétroles BP
10 quai Paul Doumer
92401 Dourbevoie

SADOUL P.
I.N.S.E.R.M., U. 14
Plateau de Brabois
54500 Vandoeuvre-lès-Nancy

SARASIN A.
Institut de Recherches
Scientifiques sur le Cancer
Centre National de
Recherche Scientifique
Boîte Postale 8
94800 Villejuif

SEBAN R.
15 rue des Marguettes
75012 Paris

SEIBEL G. M. G.
F.F.S.A.
53 rue François 1er
75008 Paris

SIMON B.
Département Médical
ESSO, S.A.F.
92080 Paris La Défense
Cedex 2

SIOU G.
Shell Française
29 rue de Berri
75380 Paris Cedex 08

SMAGGHE G.
Produits Chimiques
Ugine Kuhlmann
Boîte Postale 175
75782 Paris Cedex 16

STUPFEL M.
I.N.S.E.R.M., U. 123
44 chemin de Ronde
78110 Le Vésinet

SUCHET A.
Fondation A. de Rothschild
Service Médecine Préventive
56 avenue Mathurin Moreau
75019 Paris

SYROTA M. J.
Ministère de l'Environnement
13 rue de Bourgogne
75007 Paris

TESSIER J. F.
Laboratoire d'Hygiène
Faculté de Médecine
place de la Victoire
Bordeaux

THAL M. F.
Commissariat à l'Energie
Atomique
Département de Protection
Boîte Postale 6
92260 Fontenay-aux-Roses

TREMOLIERES J.
Laboratoire de Nutrition
Humaine
I.N.S.E.R.M.
Hôpital Bichat
170 boulevard Ney
75018 Paris

TRICARD D.
Ministère de la Santé
20 rue d'Estrées
75007 Paris

TRUCHOT A.
Compagnie Française de
Raffinage
39/43 quai André Citroën
75739 Paris-Cedex 15

TRUHAUT R.
Centre de Recherches Toxicologiques de la Faculté des
Sciences Pharmaceutiques et
Biologiques de l'Université
René Descartes
7 avenue de l'Observatoire
75006 Paris

TRUFFERT L.
7 avenue Barbès
94100 St. Maur des Fossés

TULLIEZ J.
Institut National de la
Recherche Agronomique
C.N.R.Z.
Laboratoire des Additifs
Alimentaires
78350 Jouy-en-Josas

VAREILLE J.
Laboratoire Central de la
Préfecture de Police
39 bis rue de Dantzig
75015 Paris

VEIL S.
Ministre de la Santé
20 rue d'Estrées
75007 Paris

VIAL J.
Institut Pasteur Lyon
69365 Lyon Cedex II

VILLERMAY D.
Revue de l'Infirmière
9 rue de Berri
75384 Paris Cedex 08

WARNET J. M.
62 rue Brancion
75015 Paris

WHIPPLE P.
Education Nationale
46 Avenue du Général de
Gaulle
Boîte Postale 132
49400 Saumur

YANA A.
Ministère de la Qualité
de la Vie
14 boulevard du Général
Leclerc
92521 Neuilly/Seine

ZERAFFA J.
I.N.S.E.R.M.
101 rue de Tolbiac
75013 Paris

GREECE

ZAPHIROPOULOS M.
Environmental Pollution
Control Project
Voulis 4
Athens

HELVETIA

BERGEN P.
World Wide Medical News
Service A.G.
6 rue du Léman
1201 Genève

COLLET R. A.
Université de Genève
Section de Chimie
30 que Ernest-Ansermet
1211 Genève 4

DUPUIS G.
Ciba-Geigy A.G.
4002 Basel
Rosental

HÖGGER D.
Eidg. Kommission für
Lufthygiene
8032 Zürich
Kapfstr. 16

PRIGLINGER R.
Amt der öst. Landesregierung
Sanitätsdienst
Harrachstr. 16A
4020 Linz

POLSKA

KOTLAREK-HAUS S.
Medical School
Department of Haematology
Pasteura 4
50-367 Wroclaw

LOSZEK W.
Ministerium der Schwereindustrie
00-163 Warszawa
Str.Karmelicka 15m44

WLODEK S.
Université Polytechnique
Institut de Genie de l'Environnement
00-661 Warszawa
Pl.Jednosci Robotniczej 1

REPUBLIC OF SOUTH AFRICA

van ROOYEN G. I.
Department of Health
Private Bag X88
Pretoria

REPUBLIQUE CENTRAFRICAINE

BEDAYA NGARO S.
Ministère de la Santé
Publique et des Affaires
Sociales
Bangui

MOKEMATKENGUEMBA G.
Société National
d'Habitat
Bangui

SUOMI

HERNBERG S.
Institute of Occupational
Health
Haartmaninkatu 1
00290 Helsinki 29

LAAMANEN A.
University of Kuopio
Puistokatu 20
70100 Kuopio 10

LEHTO V.-P.
Environmental Protection
Council
Secretary of Work and
Housing
Environment Section
Ministry of Internal Affairs
Fredrikinkatu 58 D 62
00100 Helsinki 10

OJAJARVI J.
Department of Public Health
Science
Haartmaninkatu 3
00290 Helsinki 29

SUMARI P.
Institute of Occupational
Health
Haartmaninkatu 1
00290 Helsinki 29

VIRTANEN I.
III Department of Pathology
University of Helsinki
Kaartmaninkatu 3
00290 Helsinki 29

VUORI E.
Department of Public Health
Science
Haartmaninkatu 3
00290 Helsinki 29

SVERIGE

ABDULLA M.
Research Department 2
University Hospital
22185 Lund

BERGLUND U. L.
Psychological Laboratories
University of Stockholm
Box 6706
11385 Stockholm

BERLIN M.
University of Lund
Department of Environmental
Health
Box 2009
22002 Lund 2

BJÖRLING M.
Saab-Scania AB
46100 Trollhätten

DANIELSON L.
Swedish Environment
Protection Board
17120 Solna 1

FRIBERG L.
Department of Environmental
Hygiene
The Karolinska Institute
10401 Stockholm 60

GAGE J. C.
Department of Environmental
Health
University of Lund
Box 2009
22002 Lund 2

HOLM S.
Department of Environmental
Health
University of Lund
Box 2009
22002 Lund 2

HOLMQVIST I.
Bolieden Aktiebolag
Bömskärsverken
93200 Skelleftehamn

KJELLSTRÖM T.
Department of Environmental
Hygiene
The Karolinska Institute
10401 Stockholm 60

LINDVALL T.
Department of Environmental
Hygiene
The Karolinska Institute
10401 Stockholm 60

PISCATOR M.
Department of Environmental
Hygiene
The Karolinska Institute
10401 Stockholm 60

RINDER L.
University of Göteborg
40033 Göteborg

SVENSSON K.
Saab-Scania AB
46100 Trollhätten

TUNISIE

ATALLAH S.
Service de l'Assainissement
Ministère de la Santé
Publique
Tunis

WILSON J. C.
Ecole Nationale des Ingénieurs de Tunis
B.P. No. 37
Tunis-Belvédère

UNITED KINGDOM

BARLTROP D.
Paediatric Unit
St. Mary's Hospital
Medical School
Norfolk Place
London W.2.

BARRATT R. S.
Chemistry Department
University of Birmingham
P.O. Box 363
Edgbaston
Birmingham B15 2TT

BARRY P.
The Associated Octel Co.
Ellesmere Port
Cheshire

BROOKS A. G. F.
Medical Research Council
Air Pollution Research Unit
St. Bartholomew's Hospital
Medical College
Charterhouse Square
London E.C.1.

BROWN P.
Elsevier North Holland
Scientific Publishers
55 Benslow Rise
Hitchin
Hertfordshire SG4 9QY

BULCRAIG W. R.
Pilkington Brothers Ltd.
R and D Department
Watson Street
St. Helens
Lancashire WA10 3TT

BURGESS J. E.
Dow Chemical Company
Huntingdon Research Centre
Estuary Road
King's Lynn
Norfolk

CERNIK A. A.
Central Reference Laboratory
Department of Employment
1 - 13 Chepstow Place
Westbourne Grove
London W.2.

CHAPMAN J.
Medical Research Council
Headquarters
20 Park Crescent
London W1N 4AL

CHARLTON J.
Environmental Services
Department
Trafalgar House
Paradise Circus Queensway
Birmingham B1 2BQ

CLARKE R. H.
Central Electricity Generating Board
Berkeley Nuclear Laboratories
Berkeley
Gloucestershire GL13 9PB

COMMINS B. T.
Medical Research Council
St. Bartholomew's Hospital
Medical College
Charterhouse Square
London EC1M 6BQ

DANIEL J. W.
Life Science Research
Stock
Essex CM4 9PE

DELVES H. T.
Department of Chemical
Pathology
Institute of Child Health
University of London
30 Guilford Street
London WC1N 1EH

DERRETT C. J.
Medical Research Council
Air Pollution Unit
St. Bartholomew's Hospital
Medical College
Charterhouse Square
London EC1M 6BQ

DUCK B. W.
British Petroleum Company
B.P. Research Centre
Chertsey Road
Sunbury-on-Thames
Middlesex

DUNCAN K. P.
British Steel Corporation
33 Grosvenor Place
London SW1X 7JG

FLOREY C. du V.
Department of Epidemiology
and Social Medicine
St. Thomas's Hospital
Medical School
60 Sancroft Street
London S.E.1.

GILTROW J.
Central Unit on Environmental Pollution
Department of the Environment
2 Marsham Street
London S.W.1.

GRIFFITH R. R.
Associated Octel Co. Ltd.
20 Berkeley Square
London W1X 6DT

HARRISON G. F.
Associated Octel Co. Ltd.
20 Berkeley Square
London W1X 6DT

HARRISON R. M.
Imperial College of Science
and Technology
Public Health Engineering
Section
Imperial Institute Road
London SW7 2BX

HEDGES W. V.
Blythe Colours Ltd.
Cresswell
Stoke-on-Trent ST11 9RD

HISCOCK S.
Lead Development Association
34 Berkeley Square
London W1X 6AJ

HISLOP J.
Environmental and Medical
Sciences Division
A.E.R.E.
Harwell
Didcot
Berkshire

2515

INTERNATIONALE ORGANISATIONEN
INTERNATIONAL ORGANIZATIONS
ORGANISATIONS INTERNATIONALES
ORGANIZZAZIONI INTERNAZIONALI
INTERNATIONALE ORGANISATIES

Preceding page blank

ECONOMIC AND SOCIAL COMMITTEE OF THE EUROPEAN COMMUNITIES

DE GRAVE M.
Avenue Charles Woeste 208
1090 Bruxelles
(Belgique)

PEEL J. H.
Warren Court Farm West
Tytherley near Salisbury
Wiltshire (United Kingdom)

EUROPEAN PARLIAMENT

KÜSTER B.
Commission Santé Publique
Centre Européen du Kirchberg
Luxembourg (Grand Duché)

FOOD AND AGRICULTURE ORGANIZATION

GRIFFITHS R. C.
Fishery and Marine Science
Officer
c/o Unesco
7 Place de Fontenoy
75007 Paris (France)

INTERNATIONAL ATOMIC ENERGY AGENCY

KOBAYASHI S.
Radiation Biology Section
Division of Life Sciences
P.O. Box 645
Kärtner Ring 11
1011 Vienna (Austria)

INTERNATIONAL LABOUR OFFICE

LARRUE M. G.
Bureau de Paris de l'Office
International du Travail
Paris (France)

Preceding page blank

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION

SIMONSGAARD V.
Dansk Standardiseringsrad
Aurehøvej 12
2900 Hellerup (Danmark)

INTERNATIONAL UNION ON HEALTH EDUCATION

ORJOLLET M.
12 rue Gustave LeBon
75014 Paris (France)

ORGANIZATION FOR ECONOMIC COOPERATION AND DEVELOPMENT

ALEXANDRE A.
2 rue André Pascal
75775 Paris-Cedex 16
(France)

HAINES J. A.
2 rue André Pascal
75775 Paris-Cedex 16
(France)

HUNTER G.
2 rue André Pascal
75775 Paris-Cedex 16
(France)

IDMAN M.
2 rue André Pascal
75775 Paris-Cedex 16
(France)

KRAMISH A.
U.S. Delegation to the
O.E.C.D.
19 rue de Franqueville
75016 Paris (France)

NOBBS C.
2 rue André Pascal
75775 Paris-Cedex 16
(France)

WYZGA R.
Central Analysis and
Evaluation Unit
2 rue André Pascal
75775 Paris-Cedex 16
(France)

UNITED NATIONS

SERWER D.
U.N. Environment Programme
Geneva Liaison Office
Palais des Nations
Geneva (Switzerland)

UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION

BATISSE M.
Département des Sciences de l'Environnement et des Recherches sur les Ressources Naturelles
7 Place de Fontenoy
75700 Paris (France)

von DROSTE B.
Division des Sciences Ecologiques
7 Place de Fontenoy
75700 Paris (France)

FREDERIKSEN M.
Section de la Recherche dans le domaine des Sciences de l'Ingénieur
7 Place de Fontenoy
75700 Paris (France)

GILBRICH W.
Division des Sciences de l'Eau
7 Place de Fontenoy
75700 Paris (France)

MAHEU R.
Director-General
7 Place de Fontenoy
75700 Paris (France)

WORLD HEALTH ORGANIZATION

DIETERICH B. H.
Division of Environmental Health
Avenue Appia
1211 Geneva 27
(Switzerland)

FALK H.
Avenue Appia
1211 Geneva 27
(Switzerland)

KÜHNER A.
Avenue Appia
1211 Geneva 27
Switzerland

KUMPF J.
Regional Office for Europe
Scherfigsvej 8
Copenhagen Ø
Denmark

LAMBO T. A.
Deputy Director General
Avenue Appia
1211 Geneva 27
(Switzerland)

TOMATIS L.
International Agency for Research on Cancer
Unit of Chemical Carcinogenesis
150 Cour Albert Thomas
69008 Lyon
(France)

VOUK V. B.
Division of Environmental Health
Avenue Appia
1211 Geneva 27
(Switzerland)

2522.k

MERLUZZI, F., 231
MICHAELSON, I.A., 805
MILIC, S., 1829, 2285
MILOVANOVIC, Lf., 2285
MIRE, B., 973
MITCHELL, C.A., 669
MITCHELL, R.I., 47, 62
MOKEMATKENGUEMBA, G., 178, 1941, 1951
MOLDOVAN, N., 1583
MOLLARET, P., 1938
MONCELON, B., 1661
MONCHAUX, G., 1189
MONKMAN, J.L., 1015, 1331
MOONEY, T.F., 1637
MOORE, M.R., 535, 1171, 2252
MOORE, W., 751
MOREAU, M., 1315
MORGADE, C., 695
MORGAN, G.B., 2073
MORRESI, N., 231
MORRIS, S.C., 677, 683
MÖSE, J.R., 1617
MOULE, Y., 967
MRAK, E.M., 1965
MURAYAMA, H., 91
MUSSENDEN, R., 833

NAGDA, N.L., 2083
NANGNIOT, P., 1675
NEEDLEMAN, H.L., 584, 1155, 1166, 1167, 1168, 1169, 1936, 2433
NEUBERGER, M., 989
NEWHOUSE, M., 383, 1263, 1953
NEWILL, V.A., 161
NIEUWSTRATEN, N., 1351
NORBACK, D.H., 385
NORSETH, T., 913
NOTTEN, W.R.F., 2047, 2059, 2060
NÜRNBERG, H.W., 2231

OLEKSYK, E., 685
OLOFFS, P.C., 702, 723, 750, 961, 1065, 1953, 2350
OMENN, G.S., 1563, 1952
OREL, J.V., 2177
ORIOL, P., 269
OTT, W.R., 2097
OUW, K.H., 1101

PACIGA, J., 1685
PACKHAM, R.F., 1468
PATTI, F., 2225
PEAT, J.K., 63
PECORA, L., 1823
PELECH, L., 279
PERROTEY, J., 1199
PERRY, R., 1285, 1328, 1385, 1405, 1783
PETERS, R., 2397
PETERSON, R.W., 3
PFANNHAUSER, W., 258, 858, 1328, 1719, 2253
PHAM, Q.T., 208, 470, 973, 988
PHILP, J.M., 2350
PICHE, L., 1314, 1468
PISCATOR, M., 830, 951, 958, 959, 1221, 2297
PITTWELL, L.R., 2303
PIVA, C., 1789
POTT, F., 715
POWELL, W., 833

PRINZ, B., 591, 1471, 1489
PTASNIK, J.A., 571

QUAGLIARDI, A., 1287
QUINOT, E., 1519

RABINOWITZ, M., 847
RAFFONELLI, A., 695
RAINSBURY, R., 2397
RALL, D., 37
RAMACIOTTI, D., 659, 2316
REAY, J.S.S., 1669
RECHT, P., 157, 1894, 1928, 1938, 1946, 1961, 2641
REEVES, A., 724, 1637, 2385
RETHFELD, H., 1407, 1416
REUSMANN, G., 591
REUTER, L., 1066
REY, P., 659, 667
ROBERTS, T.M., 1685
ROELS, H., 631, 887, 1237, 2185
ROGGI, C., 1697
RONDIA, D., 523, 535, 1339
ROOSKEN, A.A., 1351
ROOTS, L.M., 1113
van ROOYEN, G.I., 2382
ROSCA, Gh., 1073
ROSCA, S., 1073
ROSIVAL, L., 877, 1187, 1237
ROSSANO, A.T., 2083
ROSSI, A., 1823
RUBIN, R.J., 903, 911, 912
RÜDEN, H., 1757
RUDOLF, W., 2115
RUTENFRANZ, J., 2031
RÜTZEL, H., 2231
RYLANDER, R., 137, 477, 484, 667

SABATINI, G.C., 1697
SADOUL, P., 973
SALAZAR, S., 2091
SANOTSKY, I.V., 1009, 2349, 2409, 2433
SANSONI, B., 1853
SANTARONI, G.P., 1030, 1451
SANTOLUCITO, J.A., 702, 1051, 2387, 2394
SAUERHOFF, M.W., 805
SAVINO, A., 931, 1749
SAYERS, M.H.P., 1207
SCASSELLATI-SFORZOLINI G., 931, 1749
SCHALLER, K.H., 1087
SCHNEIDER, T., 1954, 2071, 2155, 2158, 2162, 2166, 2168, 2172, 2174, 2175, 2178, 2182
SCHILLING, R.S.F., 669
SCHLATTER, C., 723
SCHLIPKÖTER, H.W., 190, 228, 369, 521, 667, 723, 771, 2328
SCHMIDT, P., 279, 354
SCHOENBERG, J.B., 669
SCHUCK, E.A., 2073, 2159, 2161, 2164, 2171, 2173, 2176, 2177, 2179, 2180, 2181, 2182
SCHULLER, P.L., 1017
SCHULZ, C.O., 903
SCHWING, R.C., 1491, 1502, 1503, 2178, 2181
SCOPPA, M., 958
SEBASTIEN, P., 1189
SECCHI, G.C., 1123

SEIFERT, D., 1407
SERWER, D., 2383
EL-SEWEFY, A.Z., 1589
SHAHEEN, H., 1589
SHAMS El-DEEN, A., 1589
SHAPIRO, I.M., 1155
SHAPIRO, M.A., 677
SHERWOOD, R.J., 471, 1340, 1954
SHUVAL, H.I., 1067
SILBERGELD, E.K., 793, 814, 1051
SILVERMAN, A.P., 1601
SKJAERASEN, J., 1233
SLATER, D.H., 1783
SMEETS, J., 1087, 2185
SMIDT, U., 1557
SMITH, R.G., 1637
SMITH, G., 1729
SÕRENSEN, S., 137, 477
STANKOVIC, B., 2285
STANKOVIC, M., 2285
STANKOWSKA, K., 685
STANLEY, R., 1729
STARA, J.F., 714, 751, 771, 772, 813
STEELE, T.D., 1954, 1961, 2170
STEENSBERG, J., 472, 1006, 1960 2432
STEPANEK, V., 1473, 1478, 1503
STEPHAN, W.I., 1779
STERN, A.C., 2143
STEVENS, L., 1001
STEWART, H.N.M., 1669
STIDL, H.G., 989
STOEPPLER, M., 2231, 2259
STOOFF, W., 1479
STOPPS, G.J., 229
STUIK, E.J., 537
STUPFEL, M., 89, 770, 844, 1275, 1625. 1963, 2043
SUESS, M.J., 339
SULAIMAN, A.B., 657, 683, 1952
SUTHERLAND, L.C., 484, 485, 491
SWYNGEDOUW, I., 1131
SYROTA, M.J., 399, 457, 459, 462
SZADKOWSKI, D., 1841, 2183, 2249, 2256, 2259
SZPERLINSKI, Z., 1711

TAKABATAKE, E., 2197
TATI, M., 2251
TAYOT, J., 1199
TER HAAR, G., 803, 1177
THOMAS, R.S., 1331
THOMAS, T.J., 1569
THOMPSON, J.M., 1779
TOMATIS, L., 1053, 2317, 2328, 2329
TOMPKINS, E., 2197
den TONKELAAR, E.M., 1017, 1028, 1029, 1030
TRAKOWSKI, A.C., 2455
TREMOLIERES, J., 1902, 1921, 1927, 1944, 1950
TRUFFERT, L., 2255, 2300
TSUCHIYA, K., 2197, 2351, 2364, 2365
TULLIEZ, J., 921, 929
TUMASONIS, C.E., 879
TWIBELL, J.D., 1385, 1397, 1398
TYTUN, A., 545

VALENTA, P., 1416, 2231
VALJAREVIC, V., 1829

VANINI, G., 1289
VEIL, S., 1, 25
VERBERK, M.M., 2005
VOINIER, B., 659
VOUK, V.B., 467, 469, 473, 1912, 1925, 1930, 1931, 1947
VUORI, E., 2263, 2296

WALDBOTT, G.L., 1575
WALLER, R.E., 77, 89, 90
WANNAG, A., 1233, 1237, 1238
WARNER, P.O., 1001, 1006, 1007, 1008
WASSERMANN, D., 1053
WASSERMANN, M., 103, 156, 396, 683, 702, 713, 877, 1053, 1065, 1066, 1439, 1955
WATANABE, H., 91, 104
WEAVER, N.R., 369
WEBER, O., 260, 2261, 2295, 2297, 2299, 2301, 2302, 2303
WEICHERT, N., 1417
WEIR, F.W., 1989, 2001, 2002, 2003, 2004
WEISS, B., 2415, 2432, 2433
WESOLOWSKI, J.J., 471, 1729
WETHERILL, G.W., 847, 857, 858, 859, 1298
WILCOX, S.L., 1241
WILLIAMS, H., 1601
WILLIAMS, M.K., 551
WILLIAMS, R., 47
WISSMATH, P., 1853
WOIDICH, H., 1719
WOOLCOCK, A.J., 63
WORTH, G., 1557

YANIV, S.L., 1249, 1260
YORDANOV, D., 1815

ZAPHIROPOULOS, M., 1961
de ZEEUW, M., 1947
ZELENKO, V., 247
ZIELHUIS, R.L., 175, 364, 537, 542, 543, 692, 1040, 1100, 1168, 2002, 2060, 2348, 2384
ZUNIC, R., 2386
ZWIERS, J.H.L., 1017

REINHARDT J.
Niedersächsisches Landesverwaltungsamt - Dezernat
Arbeitsmedizin, Immissions- und Strahlenschutz
3 Hannover
Bertastr. 4

RETHFELD H.
Landwirtschaftliche Untersuchungs- und Forschungsanstalt
Joseph-König-Institut
4 Münster (Westf.)
von Esmarch-Str. 12

RICHTER E.
Institut für Pharmakologie,
Toxikologie und Pharmazie
der Tierärztl. Fakultät
8000 München 22
Veterinärstr. 13

ROSSBACH H.
Geschäftsstelle des Rates
von Sachverständigen für
Umweltfragen
62 Wiesbaden
Statistisches Bundesamt
Gustav-Stresemann-Allee 11

RUDOLF W.
Bundesstelle für Umweltangelegenheiten
6000 Frankfurt/M
Feldbergstr. 45

RÜDEN H.
Hygiene-Institut der
Universität
53 Bonn 1
Venusberg, Klinikgelände 35

SCHLIPKÖTER H. W.
Med. Institut für Lufthygiene
und Silikoseforschung an
der Universität Düsseldorf
4000 Düsseldorf
Gurlittstr. 53

SCHMIDT E.
Bundesgesundheitsamt
1 Berlin 33
Postfach

SCHMIDT K. G.
Institut für exp. Toxikologie
und Chemotherapie
69 Heidelberg
Kirschnerstr. 6

SCHOLZ G.
Stadtverwaltung Mülheim
433 Mülheim / Ruhr
Rathaus

SEYBOLD I.
BASF Farben + Fasern AG
Bereich Siegle Stuttgart
7000 Stuttgart 30
Postfach 30 06 20

STEINMANN D.
Ministerium für Wirtschaft
Mittelstand und Verkehr
des Landes NW
4 Düsseldorf
Haroldstr. 4

STOEPPLER M.
Zentralinstitut für
Analytische Chemie der
Kernforschungsanlage
Jülich GmbH
Postfach 365
517 Jülich

SZADKOWSKI D.
Zentralinstitut für Arbeitsmedizin
2 Hamburg 76
Adolph-Schönfelderstr. 5

THIEL W. R.
Verein Deutscher Ingenieure
Kommission Reinhaltung der
Luft
4 Düsseldorf 1
Postfach 1139

VALENTA P.
Zentralinstitut für
Analytische Chemie der
Kernforschungsanlage
517 Jülich
Postfach 365

WEIGAND W.
Farbwerke Hoechst A.G.
Pharma Forschung Toxikologie
6230 Frankfurt/M. 80

WITTENZELLNER R.
Gesellschaft für Strahlen-
und Umweltforschung mbH
8042 Neuherberg
Post Oberschleissheim
Ingolstädter Landstrasse 1

WOLFERMANN H.-F.
Max-Planck-Institut für
Landarbeit und Landtechnik
655 Bad Kreuznach
Am Kauzenberg

WOSING U.
Bundesgesundheitsamt
1 Berlin 33
Postfach

WUNDERER A.
Bayer A.G.
Abt. Zentrale Anwendungs-
technik
Leverkusen - Bayerwerk

CANADA

BATES D. V.
University of British
Columbia
Dean's Office
Faculty of Medicine
Vancouver, B.C.

BERNSTEIN A.D.
Medical Services Branch
Health and Welfare Canada
255 Argyle Avenue
Ottawa, Ontario K1A OL3

BUTLER G. C.
Division of Biological
Sciences
National Research Council
of Canada
Ottawa, Ontario K1A OR6

DENNIS C. A. R.
Prairie Institute of Envi-
ronmental Health
2220 Lorne Street
Regina, Saskatchewan

FINKELSTEIN B.
St. Joseph's Hospital
49 Dow Avenue
Hamilton, Ontario

GIBBS G. W.
Department of Epidemiology
and Health
McGill University
3775 University Street
Montreal, Quebec H3A 2B4

HAZUCHA M.
McGill University
Department of Physiology
3655 Drummond Street, No 1116
Montreal, Quebec

LAO R. C.
Air Pollution Control
Directorate
Environmental Health Centre
Tunney's Pasture
Ottawa, Ontario K1A 0H3

LESAGE M.
Association des Mines
d'Amiante
5 place Ville Marie
Chambre 412
Montréal, Québec

LEVY D.
812 King Street East
Hamilton, Ontario

MAREK B.
Swiss Federal Health Office
Division of Food Control
Section Pesticide Residues
and Contaminants
3000 Berne
Haslerstrasse 16

MERIAN E.
Schweiz. Arbeitsgemeinschaft für Umweltforschung
4106 Therwil
Im Kirsgarten 22

MÜLLER U.
Kantonales Laboratorium
3000 Bern 9
Postfach

RAMACIOTTI D.
Institut de Médecine Sociale et Préventive
20 quai de l'Ecole de
Médecine
1205 Genève

REY P.
Institut de Médecine Sociale et Préventive
20 quai de l'Ecole de
Médecine
1205 Genève

RINZEMA L. C.
Dow Chemical Europe SA
8832 Wollerau
Erlenstr. 46

RYLANDER R.
Institut de Médecine Sociale et Préventive
20 quai de l'Ecole de
Médecine
1205 Genève

SCHLATTER C.
Veterinär- Physiologisches
Institut der Universität
Winterthurerstr. 260
8057 Zürich

SCHLATTER-LANZ I.
Schweiz. Toxikologisches
Informationszentrum
8028 Zürich
Zürichbergstr. 8

SEILER J. P.
Eidg. Forschungsanstalt
für Obst-, Wein- und
Gartenbau
8820 Wädenswil

STAM J.
Du Pont de Nemours Int.SA
29 bis rue de Lancy
1211 Genève 24

VOUK L.
6 avenue du Lignon
Genève

HUNGARY

KÖVÁRI K.
1012 Budapest
I. Attila 107

INDONESIA

SETIADY I.
Directorate General of
Communicable Disease Control
Ministry of Health
Jl. Percetakan Negara
Post Bos 223
Jakarta

IRAN

AHMED W.
Human Environment Division
Department of Environmental Conservation
Teheran

AREFI M.
Human Environment Division
Department of Environmental Conservation
Teheran

ROUANI M.
Health Affairs
National Iranian Oil Co.
Teheran

IRELAND

CHAMBERS P.
Department of Pharmacology
University of Dublin
Trinity College
Dublin

DEAN G.
The Medico Social Research Board
73 Lower Baggot Street
Dublin 2

DUGGAN C.
An Taisce
The National Trust for Ireland
Warrenscourt
Lissarda
County Cork

GRIMES H.
Department of Pathology and Bacteriology
Regional Hospital
Galway

HEAGNEY J. K.
North Western Health Board
Kintogher
Bundoran Road
Sligo

HICKEY N.
Department of Social and Preventative Medicine
University College
Earlsfort Terrace
Dublin 2

KEVANY J.
Trinity College Medical School
St. James's Hospital
Dublin 8

ISRAEL

WASSERMAN M.
Department of Occupational Health
The Hebrew University
Hadassah Medical School
P.O. Box 1172
Jerusalem

HOLLAND W. W.
Department of Clinical
Epidemiology and Social
Medicine
St. Thomas's Hospital
Medical School
London SE1 7EH

HOWE D.
Paintmakers Association
of Great Britain
22 Hightree Drive
Henbury
Macclesfield
Cheshire

HUGHES E. G.
Johnson, Matthey & Co. Ltd.
78 Hatton Garden
London EC1P 1AE

HUNTER W. J.
General Foods Europe
Banbury OX16 7QU

INGIMUNDARSON E. V.
National Institute of
Environmental Health
Bernard Sunley House
40-44 Evelyn Gardens
London S.W.7.

IRWIG L.
Department of Clinical
Epidemiology and Social
Medicine
St. Thomas's Hospital
Medical School
London SE1 7EH

JACOBSEN M.
Institute of Occupational
Medicine
8 Roxburgh Place
Edinburgh EH8 9SU

KING E.
National Occupational
Hygiene Service Ltd.
12 Brook Road
Fallowfield
Manchester

LEEDER S.
Department of Clinical
Epidemiology and Social
Medicine
St. Thomas's Hospital
Medical School
London SE1 7EH

LEESE W. L. B.
Mobil Oil Corporation
54 - 60 Victoria Street
London S.W.1.

LEMON R. C.
Shell International
Petroleum Co.
Medical Division
Shell Centre
London SE1 7NA

McNEIL N.
Scottish Home and Health
Department
St. Andrew's House
Edinburgh

MARTIN A. E.
Department of Health and
Social Security
Alexander Fleming House
Elephant and Castle
London SE1 6BY

MILLER D. S.
Department of Community
Health and Medicine
Medical School
Nottingham University
Nottingham NG7 2RD

MILLS A. L.
Burmah-Castrol Company
Castrol Research Laboratories
London Road
Bracknell
Berkshire RG12 2UW

MOORE J. P.
Occupational Hygienist
Shell International
Petroleum Co.
Medical Division
Shell Centre
London SE1 7NA

MOORE M. R.
Department of Materia Medica
Stobhill General Hospital
Glasgow G21 3UW

MOORHOUSE J.
Rio Tinto-Zinc Corporation
6 St. James's Square
London SW1Y 4LD

MULLINS C.
Instrumentation Laboratory
(U.K.) Ltd.
Station House
Stamford New road
Altrincham
Cheshire

OLDHAM P. D.
MRC Pneumoconiosis Unit
Llandough Hospital
Penarth
Glamorgan CF6 1XW

PACKHAM R. F.
Water Research Centre
Medmenham Laboratory
Ferry Lane
Medmenham
Marlow
Buckinghamshire SL7 2HD

PERRY R.
Imperial College of Science
and Technology
Public Health Engineering
Section
Imperial Institute Road
London S.W.7.

PHILP J. McL.
Unilever Limited
Unilever House
P.O. Box 68
London EC4P 4BQ

PITTWELL L. R.
Department of the Environment
Directorate General of
Water Engineering
2 Marsham Street
London SW1P 3EB

PURI G.
Liverpool Polytechnic
Department of Biology
Byrom Street
Liverpool 3

RAINSBURY R.
British Medical Journal
BMA House
Tavistock Square
London W.C.1.

RATCLIFFE J. M.
Imperial College of Science
and Technology
Department of Mathematics
London S.W.7.

REED S. B.
Greater London Council
40 Brynmaer Road
London SW11 4EW

SAYERS M. H. P.
Department of Employment
Central Reference Laboratory
1 - 13 Chepstow Place
Westbourne Grove
London W.2.

SHERWOOD R. J.
Honey Bottom
Dry Sandford
Abingdon
Oxfordshire OX13 6BX

SILVERMAN A. P.
Imperial Chemical Industries
Industrial Hygiene Research
Laboratories
Alderley Park
Near Macclesfield
Cheshire SK10 4TJ

STANLEY F.
Medical Research Council
Social Medicine Unit
London School of Hygiene
and Tropical Medicine
Gower Street
London W.C.1.

COMMISSION OF THE EUROPEAN COMMUNITIES

AMAVIS R.
Direction Protection sanitaire
Centre Louvigny
23 Avenue Monterey
Luxembourg (Grand-Duché)

ANGELLETTI L. M.
C.E.N., D.P.S.
Boîte Postale 6
92260 Fontenay-aux-Roses
(France)

BATTI R.
C.E.N., D.P.S.
Boîte Postale 6
92260 Fontenay-aux-Roses
(France)

BERAUD R. C.
Service Juridique
B/11-64
200 rue de la Loi
1040 Bruxelles
(Belgique)

BERLIN A.
Direction Protection sanitaire
Centre Louvigny
23 Avenue Monterey
Luxembourg (Grand-Duché)

BERTINCHAMPS A. J.
Direction Générale de la Recherche, Science et Education
200 rue de la Loi
1040 Bruxelles
(Belgique)

BIGLIOCCA C.
C.C.R. Euratom
21020 Ispra
Varese (Italia)

BOURDEAU P.
Direction Générale de la Recherche, Science et Education
200 rue de la Loi
1040 Bruxelles
(Belgique)

CARPENTIER M.
Service Environnement
200 rue de la Loi
1040 Bruxelles
(Belgique)

DEL BINO G.
Service Environnement
200 rue de la Loi
1040 Bruxelles
(Belgique)

DEPAUS R.
C.C.R. Euratom
Petten
(Netherlands)

DI FERRANTE E.
Direction Générale de la Recherche, Science et Education
200 rue de la Loi
1040 Bruxelles
(Belgique)

FACCHETTI S.
C.C.R. Euratom
Chemistry Division
21020 Ispra
Varese (Italia)

GAGLIONE P.
C.C.R. Euratom
21020 Ispra
Varese (Italia)

GEISS F.
C.C.R. Euratom
21020 Ispra
Varese (Italia)

GIBB J. M.
Direction Général de l'Information Scientifique et Technique et Gestion de l'Information
29 rue Aldringen
Luxembourg (Grand-Duché)

HENTZ P.
Direction Sécurité et Médecine de Travail
Centre Louvigny
23 Avenue Monterey
Luxembourg (Grand-Duché)

HILLERY P. J.
Vice-Président
200 rue de la Loi
1040 Bruxelles
(Belgique)

KARCHER W.
C.C.R. Euratom
Petten
(Netherlands)

KARHAUSEN L.
C.E.N., D.P.S.
Boîte Postale 6
92260 Fontenay-aux-Roses
(France)

MAGNAVAL R.
C.E.N., D.P.S.
Boîte Postale 6
92260 Fontenay-aux-Roses
(France)

MÜLLER W.
C.E.N., D.P.S.
Boîte Postale 6
92260 Fontenay-aux-Roses
(France)

MUNTAU H.
C.C.R. Euratom
21020 Ispra
Varese (Italia)

OTT H.
Direction Général de la
Recherche, Science et
Education
200 rue de la Loi
1040 Bruxelles
(Belgique)

RECHT P.
Direction Protection
sanitaire
Centre Louvigny
23 Avenue Monterey
Luxembourg (Grand-Duché)

SCHORN H.
C.E.N., D.P.S.
Boîte Postale 6
92260 Fontenay-aux-Roses
(France)

SCOPPA P.
C.C.R. Euratom
Gruppo di Biologia
21020 Ispra
Varese (Italia)

SHANKS M.
Directorate General for
Social Affairs
200 rue de la Loi
1040 Bruxelles
(Belgique)

SMEETS J.
Direction Protection
sanitaire
Centre Louvigny
23 Avenue Monterey
Luxembourg (Grand-Duché)

TREU-RICCO' G.
Direction Protection
sanitaire
Centre Louvigny
23 Avenue Monterey
Luxembourg (Grand-Duché)

VAN DER VENNE M.
Direction Protection
sanitaire
Centre Louvigny
23 Avenue Monterey
Luxembourg (Grand Duché)

2522.L

SALES OFFICES

Belgique — België

Moniteur belge — Belgisch Staatsblad
Rue de Louvain 40-42 — Leuvenseweg 40-42
1000 Bruxelles — 1000 Brussel
Tél. 512 00 26
CCP 000-2005502-27 —
Postrekening 000-2005502-27

Sous-dépôt — Agentschap :

Librairie européenne — Europese Boekhandel
Rue de la Loi 244 — Wetstraat 244
1040 Bruxelles — 1040 Brussel

Danmark

J.H. Schultz — Boghandel
Møntergade 19
1116 København K
Girokonto 1195
Tel. 14 11 95

Deutschland (BR)

Verlag Bundesanzeiger
5 Köln 1 — Breite Straße — Postfach 108 006
Tel. (0221) 21 03 48
(Fernschreiber : Anzeiger Bonn
08 882 595)
Postscheckkonto 834 00 Köln

France

Service de vente en France des publications des Communautés européennes
Journal officiel
26, rue Desaix
75 732 Paris — Cedex 15
Tél. (1) 578 61 39 — CCP Paris 23-96

Ireland

Stationery Office

Beggar's Bush
Dublin 4
Tel. 68 84 33

Italia

Libreria dello Stato
Piazza G. Verdi 10
00198 Roma — Tel. (6) 8508
CCP 1/2640
Telex 62008
Agenzie :
00187 Roma - Via XX Settembre
(Palazzo Ministero
del Tesoro)
20121 Milano - Galleria
Vittorio Emanuele
3 — Tel. 806406

Grand-Duché de Luxembourg

Office des publications officielles des Communautés européennes

5, rue du Commerce
Boîte postale 1003 — Luxembourg
Tél. 49 00 81 — CCP 191-90
Compte courant bancaire :
BIL 8-109/6003/300

Nederland

Staatsdrukkerij- en uitgeverijbedrijf

Christoffel Plantijnstraat,
's-Gravenhage
Tel. (070) 81 45 11
Postgiro 42 53 00

United Kingdom

H.M. Stationery Office

P.O. Box 569
London SE1 9NH
Tel. 01-928 6977, ext. 365

United States of America

European Community Information Service

2100 M Street, N.W.
Suite 707
Washington, D.C. 20037

Tel. 296 51 31

Schweiz — Suisse — Svizzera

Librairie Payot

6, rue Grenus
1211 Genève
Tél. 31 89 50
CCP 12-236 Genève

Sverige

Librairie C.E. Fritze

2, Fredsgatan
Stockholm 16
Post Giro 193, Bank Giro 73/4015

España

Libreria Mundi-Prensa

Castelló 37
Madrid 1
Tel. 275 46 55

Other countries

Office for Official Publications of the European Communities

5, rue du Commerce
Boîte postale 1003 — Luxembourg
Tél. 49 00 81 — CCP 191-90
Compte courant bancaire :
BIL 8-109/6003/300